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NATIONAL INSTITUTES OF HEALTH

# PLAN FOR HIV-RELATED RESEARCH

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Office of AIDS Research

National Institutes of Health

U.S. Department of Health and Human Services



## CHAPTER 1

# Foundational Research



**AREA OF EMPHASIS**

# Natural History and Epidemiology

**SCIENTIFIC OBJECTIVES AND STRATEGIES****OBJECTIVE–A**

Characterize the risk factors and mechanisms of HIV transmission in domestic and international populations to guide prevention and treatment strategies.

(The scientific objectives of A, B, and C are of equal weight.)

**STRATEGIES**

- Utilize existing cohorts, including incidence cohorts, to further assess HIV transmission and acquisition.
- Model how results from existing cohorts might be altered in socioeconomically and demographically different populations (specifically based upon race, ethnicity, gender, age, and resource-rich and -poor settings).
- Conduct studies on the molecular epidemiology and the effects on HIV transmission of infection with different HIV subtypes, routes and modes of transmission, antiretroviral (ARV)-resistant viruses, multiple subtypes, and recombinant viruses.
- Conduct epidemiological and modeling research to improve estimates of per-contact risk of HIV transmission over the course of the disease process, from acute infection to onset of advanced HIV disease.
- Evaluate sexual and blood-borne HIV transmission and acquisition in relation to the following:
  - ▶ Viral factors such as viral quantity (measures of viral RNA and other quantification methods) in various body compartments (e.g., blood, saliva, and mucosal compartments), viral diversity (intrapatient diversity), and HIV genotype, including subtypes, recombinants, resistance mutants, and dual virus infections;
  - ▶ Host factors such as age, sex, hormonal status, strength and breadth of immune response, mental health, patterns of alcohol and drug use, and host genetic factors;
  - ▶ Modifiable host factors such as diet and nutritional status; drug, alcohol, and tobacco use; use of exogenous hormones; use of traditional medicines, herbal medicines, and supplements; other infections, including oral infections; other causes of mucosal pathology, including sexually transmitted diseases (STDs); and circadian rhythm;
  - ▶ Biological, behavioral, cultural, and environmental determinants of susceptibility to HIV acquisition and progression among women and girls;
  - ▶ Persistent exposure to HIV (i.e., in HIV-discordant couples);
  - ▶ Use of microbicides and barrier devices;
  - ▶ Social, cultural, behavioral, and ecologic factors, including such demographic characteristics as socioeconomic status, race, ethnicity, gender, culture, religion, community, and geographic location (e.g., rural, urban, suburban);

- ▶ Sexual activity, abstinence, partner selection, partner concurrency, sexual networks, duration of partnership, marital fidelity, control of STDs, hygienic practices, contraception choices, and cultural practices such as use of traditional vaginal preparations, female genital mutilation, and male circumcision; and
- ▶ Extent to which environmental and other macro-level factors such as war, migration, refugee status, homelessness, drug trafficking patterns, political will, and disasters influence vulnerability, risk behaviors, acquisition, and access to care in developed and developing countries.
- Conduct studies (including community-based studies) to understand and quantify the effect on HIV transmission and HIV incidence of widespread use of antiretroviral therapy (ART) by eligible individuals.
- Study the impact of widespread ART availability and resulting viral load suppression on patterns of risk behavior.
- Develop and evaluate effective interventions aimed at HIV infected persons and their partners to promote behaviors that prevent acquisition and transmission of HIV.
- Conduct community-based participatory studies that assess the impact of community mobilization on prevention and treatment success.
- Study and quantify the impact on HIV transmission of adherence to ART and related factors such as therapy and regimen characteristics, drug characteristics, and symptom management.
- Conduct epidemiological studies on the role of coinfection and comorbidity with other microbial agents in modifying the acquisition and course of HIV infection and in predicting the evolution of particular HIV/AIDS epidemics. Research should focus on hepatitis GB virus C (GBV-C), *M. tuberculosis* (TB), *Plasmodium sp.* (malaria), human papillomavirus (HPV), Epstein-Barr virus (HHV-4/EBV), hepatitis C (HCV), herpes simplex virus (HSV-1 and HSV-2), herpesvirus type 8 (HHV-8/KSHV), or other sexually or nonsexually transmitted conditions within existing programs and settings (e.g., mother-to-child transmission [MTCT]).
- Evaluate the impact on HIV transmission and disease progression of hormonal contraceptives and replacement therapies, composition of such therapies, pharmacokinetics, and duration of action of repository-form contraceptives.
- Examine the effects of vaccine trials on HIV transmission characteristics, including the effects on the alteration of transmission by vaccine-induced immunity. Examine the clinical course and markers of infectiousness among vaccine trial participants with breakthrough HIV infection to determine the vaccine's effect on viral load, rates of progression, and on population HIV incidence.
- Examine the effects of oral chemoprophylaxis (PREP) and microbicides trials on HIV transmission characteristics, including viral load setpoints and viral drug resistance.
- Conduct studies on medication-assisted substance abuse treatment modalities and access to service (e.g., methadone maintenance, buprenorphine/naloxone, naltrexone, antabuse, acamprosate, and stimulant abuse therapy), alone or in combination with mental health and/or behavioral interventions, as HIV prevention interventions, and examine their effects on HIV disease progression, adherence to ART, and acceptance of care and treatment.
- Identify effective individual, network, and community-level interventions and determine the coverage needed to decrease HIV incidence in developing and developed countries.

- Further define the timing, mechanisms, and risk factors in perinatal and postnatal transmission, including treatment of the mother, infant feeding modalities, physiology of lactation, long-term effects of perinatal interventions, maternal and infant genetic variation, and kinetics of viral resistance.
  - ▶ Define how the physiology of lactation affects HIV transmission.
  - ▶ Assess the impact of maternal ARV regimens of different potency and duration on MTCT of HIV and on the short- and long-term health of women and their children who are eligible for ART.
  - ▶ Study the safety and effectiveness of low-cost, sustainable approaches to prevention of MTCT of HIV, including exclusive breastfeeding in the first months of life with rapid weaning, and determine the effects of such approaches on infant morbidity and mortality.
  - ▶ Assess the impact of environmental factors, mental health, comorbidities, and coinfections on the risk for postnatal infection.
  - ▶ Assess the impact of perinatal treatment and prophylaxis regimens on emergence of ARV drug resistance in the mother and in those infants who become infected despite prophylaxis.
  - ▶ Assess the impact of maternal ART on HIV transmission during pregnancy and lactation.
  - ▶ Assess the impact of maternal and infant adherence to ARV regimens on the effectiveness of MTCT, the risk of subsequent ARV resistance, and the effectiveness of ART in mothers and their children.
  - ▶ Assess the impact of perinatal treatment and prophylaxis regimens on communitywide HIV resistance to ARVs.
  - ▶ Determine the impact of ARV resistance on perinatal transmission and pediatric infection.
  - ▶ Assess the impact of MTCT programs on public health measures, including maternal, paternal, and infant morbidity/mortality rates; overall life expectancy; disability-adjusted life years; and child developmental milestones.
  - ▶ Assess the impact of maternal ARV use for MTCT on morbidity in HIV-uninfected infants and children.

## OBJECTIVE-B

Use epidemiological research in domestic and international settings to identify the influence of therapeutics and other biological (e.g., age, host genetics, coinfections, HIV subtypes) and behavioral (e.g., access to and use of health care system, adherence) factors on HIV progression and response to therapy, as shown by virologic, immunologic, and clinical outcomes.

(The scientific objectives of A, B, and C are of equal weight.)

## STRATEGIES

### Strategies Related to Disease Progression and Response to ART

- Investigate the contribution of innate host characteristics to viral measures, immune function, disease progression, and mechanisms for these effects (including host genetic factors and their modulators, sex, race, and age).
- Examine how chronic inflammatory processes (and such mediators as inflammatory cytokines) that result from HIV and other concurrent infections, stress, depression, or behaviors (e.g., smoking) modify immune function, disease outcomes and survival, and response to ART.
- Assess the effect of treatment for HIV on the incidence and pathogenesis of cancer. Leverage international cohorts to characterize the impact of host genetics, environmental factors, standard-of-care treatment, and HIV subtypes on the full spectrum of cancers observed in HIV-positive individuals.
- Characterize the changing spectrum of clinical outcomes (morbidity and mortality), including causes of death associated with evolving therapeutic strategies, domestically and internationally.
- Elucidate the pathogenic mechanisms that influence residual HIV replication in ART recipients.
- Investigate the effect on disease progression of viral factors, including viral clade/subtype, fitness, viral tropism, and innate and acquired genotypic and phenotypic resistance to ARVs.
- Determine the global patterns of viral resistance (innate and acquired) to ART and how these patterns could influence the long-term effectiveness of these therapies.
- Define the prevalence and incidence of HIV-associated nephropathy, its predictors, and its influence on mortality and response to ART, domestically and in developing countries.
- Define the prevalence and incidence of HIV-associated neurologic, behavioral, and psychiatric manifestations and their relation to disease progression and response to ART, both nationally and internationally.
- Identify, characterize, and determine the frequency, changing manifestations, and effects of HIV-related respiratory disease on morbidity, mortality, and HIV disease progression (e.g., immune reconstitution syndromes affecting the lungs [including sarcoidosis], HIV-related pulmonary hypertension, accelerated emphysema, and coinfections) in domestic and international populations, including both untreated patients and those receiving ART.
- Develop new cohorts and maintain long-term followup of existing cohorts, including observational cohorts and intervention populations, to determine the changing spectrum of HIV disease and evaluate interventions, especially in minority populations and developing countries.
- Characterize the epidemiology of those recently HIV infected, including host and viral genetic characteristics, and continue to characterize the epidemiology of HIV/AIDS among those who have minimal exposure to ART,

those who have virologic and/or immunologic responses to these therapies, and those who have experienced failure of these therapies.

- Conduct studies on the pharmacogenomic determinants of the distribution and fate of ARV drug distribution throughout body compartments and of the treatment response in racially and ethnically diverse populations, as well as populations with body mass indices in the underweight, overweight, and obese ranges.

### **Strategies Related to Complications of Therapy**

- Identify the effects of ARV therapies, treatment strategies, and pharmacogenetics on disease outcomes, including (1) other HIV-associated diseases, such as central and peripheral nervous system conditions; (2) other infectious diseases; and (3) noninfectious comorbid conditions and diseases, including lipoatrophy, hyperlipidemia, diabetes mellitus, hypertension, osteopenia/osteoporosis, and steatosis, and long-term disease outcomes, including liver failure, renal failure, bone marrow suppression, malignancies, and atherosclerosis and related cardiovascular diseases.
- Identify the ART-associated toxicities (over and above metabolic syndrome) in special populations, including coinfecting populations (e.g., TB), pregnant women, pediatrics, populations receiving traditional medicines, and according to nutritional status.
- Investigate the role of coinfections, particularly HCV, on metabolic disorders commonly associated with ART.
- Investigate the role of chronic inflammation as a result of multiple chronic infections, such as HIV and HCV, or other chronic conditions, such as autoimmune disease, on metabolic disorders commonly associated with ART.
- Assess the effect of other non-ART interventions (e.g., statin use, cancer treatment) that are often used to treat the complications of ART on disease outcomes and survival.

### **Strategies Related to Comorbidities**

- Intensify research on the spectrum of HIV-associated malignant diseases that may develop in HIV infected patients who have responded to ART and are expected to live longer with subclinical immune deficiency.
- Establish normative data for lymphocyte subsets, total white blood cell count, and total lymphocyte count, and determine the influence of common comorbidities, especially malaria, TB, and helminth infection, on the "normal" values in patients from different regions of the developing world particularly affected by the HIV epidemic, such as Africa and Asia.
- Investigate TB–HIV interactions, including the effects of dual infection on the infectiousness and progression of both TB and HIV and the effect of various treatment strategies on disease control.
- Evaluate the impact of treatment of alcohol abuse, drug abuse, and mental health disorders on the effectiveness of ART, including in the context of specific forms of drug use.
- Assess the effect of HIV on other infections (e.g., hepatitis B [HBV], HCV, GBV-C, other blood-borne infections, cytomegalovirus [CMV], JC virus, HPV, EBV, KSHV, TB, HSV, and malaria and other parasitic diseases) and the effect of these infections and their treatment on HIV outcomes.
- Study the emergence and reemergence of infectious diseases and the development of antimicrobial-resistant infections (e.g., multidrug-resistant TB, sulfa-resistant malaria, antibiotic-resistant pneumococcus, cotrimoxazole-resistant *Pneumocystis carinii* pneumonia [PCP], methicillin-resistant *Staphylococcus aureus* [MRSA], and lamivudine-resistant HBV) in HIV infected populations.

- Encourage epidemiological studies of dual infection with HIV and HCV, and incorporate research on HCV infection within existing programs of research on HIV/AIDS.
- Evaluate the effectiveness of HPV vaccines among HIV-positive individuals from geographically diverse regions.
- Assess the effect of other non-ART interventions (e.g., statin use, cancer treatment) on disease outcomes and survival.

#### **Strategies Related to MTCT and Pediatric Infection**

- Study HIV infected and uninfected children and adolescents to determine factors related to impaired growth and neurodevelopment, cognitive development, impact of other childhood infectious diseases, and safety and efficacy of immunizations, and how these may be affected by medical and behavioral interventions.
- Evaluate the long-term complications of maternal and infant ART among exposed, HIV uninfected children.
- Examine the effect of the health status of HIV infected mothers and of ART during pregnancy and lactation on survival of their children, both HIV infected and uninfected.
- Investigate the long-term outcome of complications due to HIV and ART use in HIV infected pediatric populations as these children reach adolescence and adulthood.

#### **Strategies Related to Aging**

- Investigate the relationship between HIV infection and other comorbidities (HIV-associated and non-HIV-associated) that increase with aging, such as cancer, obesity, diabetes, hypertension, anemia (unexplained and anemia of chronic inflammation), emphysema, renal insufficiency, and hyperlipidemia, on disease outcomes (e.g., liver disease, cardiovascular disease, and renal disease) and survival.
- Study the incidence and determinants of physical and cognitive decline in aging HIV infected individuals, and the effect of frailty and functional impairment on HIV, ARV use, and self-care behaviors.
- Characterize the changing spectrum of clinical outcomes, including cancers, in the treated, chronically infected, aging, HIV infected populations living with prolonged immune suppression.
- Evaluate immunologic and virologic HIV disease progression and mortality in older versus younger adults on ART to identify treatment guidelines for older HIV infected patients.
- Study the effect of HIV and ART (e.g., response to treatment, adverse effects) in aging populations with coexisting morbidities and polypharmacy.

#### **Strategies Related to Adherence, Access, and Quality of Life**

- Study determinants of adherence to ART and adverse events of such therapies in all age groups in domestic and international settings.
- Study the impact of access to ART, microbicides, and vaccines on risk behaviors and HIV acquisition among at-risk populations.
- Investigate how different patterns of access, adherence, and exposure to ART in treatment-experienced and treatment-inexperienced populations contribute to ARV resistance and disease progression.

- Identify the individual and provider factors, and communication and joint decisionmaking among them, as well as infrastructure factors associated with initiating, continuing, adhering to, and discontinuing ART, and evaluate the impact of these factors on therapeutic outcomes.
- Evaluate the effects of modifiable host characteristics, specifically behavioral characteristics including adherence, mental health, substance use, sexual behavior, and cultural practices, on viral measures, immune function, disease progression, and mechanisms for these effects.
- Elucidate the effects of HIV infection on sleep disturbances, including prevalence, possible immunological and endocrine mechanisms, associations with HIV outcomes, possible changes with ART, and influence on quality of life and cardiovascular health.

## **OBJECTIVE–C**

**Develop and evaluate methods and resources for HIV/AIDS epidemiological and clinical studies that use culturally appropriate approaches; incorporate new laboratory, sampling, and statistical methods with information systems; and better integrate research findings into clinical practice and regional, national, and international policy.**

(The scientific objectives of A, B, and C are of equal weight.)

## **STRATEGIES**

- Evaluate and promote the use of study designs that incorporate appropriate ethical, cultural, and policy context for HIV/AIDS studies in diverse domestic and international populations.
- Capitalize on existing sources of data by supporting harmonization efforts in existing observational and clinic cohorts.
- Ensure that the population composition of domestic epidemiological studies reflects the shifts in the populations at risk for and affected by HIV/AIDS, including older Americans, adversely affected minorities, and those with other comorbidities.
- For studies in both domestic and international settings, improve approaches for recruitment and retention of underrepresented populations, including minorities, children, adolescents, women, drug and alcohol abusers, incarcerated populations, and persons living with mental illness.
- Support training and mentorship of medical and health professionals from communities disproportionately affected by the epidemic, both in developing countries and domestically, in the areas of research ethics, study design, informatics, data management and analysis, and linking research trials to clinical care and clinical care to health policy and implementation.

### **Strategies Related to Natural History/Pathogenesis**

- Develop epidemiologic and laboratory-based methods in conjunction with prospective cohort studies, domestically and in developing countries, to monitor response to ART and the incidence of metabolic complications related to chronic use of antiretrovirals, including:
  - ▶ Encourage development of and evaluate accurate, reproducible, and inexpensive virologic, immunologic, bacteriologic, pharmacologic, and genetic assays suitable for large-scale epidemiological research and surveillance in developing nations. Emphasis should be on simple and reliable staging of disease progression for the initiation and monitoring of ART and opportunistic infection (OI) prophylaxis; HIV resistance testing; and noninvasive diagnostic assays for STDs, other OIs including TB, and AIDS-related malignancies.
  - ▶ Develop new epidemiological designs and statistical methods, including development of informatics tools, to better characterize transmission dynamics and monitor long-term trends in disease progression and development of toxicities in the setting of potent ART.
  - ▶ Develop, maintain, and effectively cultivate ongoing and newly developed cohort studies, domestic or international specimen repositories, and databases for interdisciplinary HIV-related studies. Nested studies that utilize these resources should be particularly encouraged and developed.

- ▶ Use observational data to better characterize the natural and treated history of AIDS-associated conditions in international settings and trends in the epidemiology of these conditions.
- ▶ Develop methods for assessing HIV-related symptomatology (e.g., pain, fatigue) and quality of life that are feasible and culturally appropriate.
- ▶ Develop uniform assessment tools to measure host and environmental characteristics, including substance abuse and mental health, which may impact immediate and long-term HIV-related health outcomes. Assessment tools should be culturally appropriate without the loss of scientific validity.

### **Strategies Related to Interventions**

- Study the various operational strategies that can be employed to “bring to scale” ART programs, including the use of operations research and integrated observational databases to evaluate treatment effectiveness at the individual, community, and population levels.
- Assess the effectiveness and comparability of clinical versus laboratory monitoring for the initiation, monitoring, and switching of ART, particularly in resource-poor settings, including laboratory monitoring with new methods that are technologically and cost-appropriate to the various international settings.
- Develop appropriate clinical and laboratory definitions of short- and long-term ARV failure, and develop mechanisms for monitoring and assessing drug resistance evolution in HIV-1 variants and subtypes in domestic as well as international settings.
- Develop, evaluate, and promote new, improved, and cost-effective methods to prevent HIV transmission via blood transfusion, medical treatments, and other iatrogenic exposures in developing countries, including instrument sterilization.
- Assess the impact of different strategies for HIV testing and their linkage to care.
- Develop and refine simulation strategies (modeling) of the impact of interventions on HIV transmission, cofactors of HIV infection, and communitywide morbidity and mortality, including non-HIV infected individuals (i.e., survival of uninfected infants).

### **Strategies Related to Policy**

- Evaluate the long-term clinical and nonclinical impact, cost, and health care utilization impact of different strategies for care, including treatment of AIDS-associated conditions (e.g., OIs, anemia) and ART.
- Improve methods for disseminating research, make research results more accessible to all stakeholders, and provide the scientific basis for regional and national standards of care as well as formal HIV best practice guidelines.
- Develop formal methods to assess the applicability and transportability of guidelines for care of HIV infected individuals across countries.
- Support HIV policy research, including economic studies, necessary for translating epidemiological and clinical studies into policy.
- Encourage development of best care guidelines and national policy papers for the treatment and management of cancers in HIV infected individuals in low- and middle-resource settings.



## AREA OF EMPHASIS

# Etiology and Pathogenesis

## SCIENTIFIC OBJECTIVES AND STRATEGIES

### OBJECTIVE–A

Delineate the viral, host, and immune mechanisms involved in the transmission, establishment, and spread of HIV infection in diverse populations across the spectrum of age and gender in national and international settings.

(The scientific objectives A and B are of equal weight.)

### STRATEGIES

- Determine the role of phenotype/genotype/fitness and dose on transmission of cell-free and cell-associated HIV, in various bodily fluids at different portals of entry.
  - ▶ Define the role of cell-free and cell-associated HIV in various modes of transmission.
  - ▶ Determine the mechanisms by which virus-encoded genes and viral gene products regulate HIV infection and replication, and influence transmission, establishment, and spread of HIV infection.
  - ▶ Delineate the mechanisms by which host-encoded genes and gene products regulate HIV infection and replication, and influence the transmission, establishment, and spread of HIV infection.
  - ▶ Determine the structures of and interactions between viral and host proteins that are important for the transmission, establishment, and spread of HIV infection.
  - ▶ Determine the cell subsets and tissue types that serve as portals of entry and dissemination of HIV and that support replication during different stages of infection.
- Delineate the mechanisms by which innate and adaptive immunity influence HIV replication and modulate transmission, establishment, and spread of HIV infection.
- Investigate the role of inflammation and its mediators in tissue on HIV transmission and dissemination.
- Delineate the mechanisms by which sexually transmitted infections (STIs) and coinfections influence HIV transmission, replication, establishment, and spread of HIV infection.
- Evaluate the influence of prevention and treatment on the early events in HIV transmission, establishment, and spread.

### To facilitate the research goals listed above:

- Facilitate the translation of new insights from structural biology, computational biology, genomics, and proteomics to understand the etiology and pathogenesis of HIV infection.

- Further develop and utilize experimental human, nonhuman, *ex vivo*, and theoretical/mathematical models to study the transmission and establishment of HIV/SIV (simian immunodeficiency virus) infections with emphasis on models of direct relevance to human HIV infection and models that address important issues not readily approachable in human subjects.
- Promote augmented access to and sharing of key patient samples, animal model resources, laboratory reagents, new technologies and equipment, information databases, and quantitative as well as functional virologic and immunologic assays.
- Support and expand innovative research on the transmission, establishment, and spread of HIV infection.
- Develop and utilize natural and innovative technologies to procure, maintain, and expand the macaque model of AIDS and facilitate collaborative research using this model.

## OBJECTIVE–B

**Delineate the viral and host mechanisms associated with the pathogenesis of immune dysfunction and disease progression in diverse populations across the spectrum of age and gender in national and international settings.**

(The scientific objectives A and B are of equal weight.)

## STRATEGIES

- Define the factors that regulate initial HIV replication, control virus during primary infection, and establish viral setpoint.
- Determine how early events that regulate the establishment and systemic spread of HIV infection define the later clinical course of the disease in HIV infected populations.
- Define the viral, host, pharmacologic, copathogens, and environmental factors that contribute to disease progression and nonprogression.
- Define the virologic and host factors that enable HIV to establish and maintain a persistent infection *in vivo* in the setting of both drug-naïve and drug-treated individuals.
- Delineate the mechanisms of host immune control of HIV replication and investigate how the effectiveness of immune control may vary through the course of infection, depending on the identity and location of infected host cells and the influence of therapeutic interventions.
- Delineate the molecular mechanisms by which virus-encoded genes, viral gene products, host cellular factors, and intracellular compartments regulate HIV replication and influence pathogenesis.
- Determine the factors that influence the susceptibility of target cells to HIV infection and their ability to support HIV replication.
- Determine the structures of complexes between viral proteins and host factors involved in the processes that underlie HIV disease progression.
- Delineate the direct and indirect mechanisms underlying HIV-induced depletion and dysfunction of immune cells and tissues in humans and nonhuman primate (NHP) models, focusing on:
  - ▶ the loss of specific CD4+ T lymphocyte subpopulations and clones;
  - ▶ the impact of HIV infection on T-cell population numbers, specificities, and functions;
  - ▶ HIV-triggered immunopathogenesis, including immune activation, cell death, induction of nonresponsiveness, dysregulation in the number and function of immune effector cells other than T lymphocytes, and production of host factors, including cytokines and other mediators;
  - ▶ the structural and functional compromise of primary and secondary lymphoid organs including hematopoietic precursor cells and their microenvironment;
  - ▶ influences on the developing immune system; and
  - ▶ disruption of host compensatory mechanisms that govern the generation, regeneration, and homeostasis of T-cell populations.

- Evaluate whether and to what extent viral-induced damage to the systemic and mucosal immune systems can be reversed following suppression of HIV replication by therapeutic interventions.
- Determine the lifespan and developmental and regenerative pathways of T lymphocytes in humans and NHP models; elucidate the mechanisms that regulate the size and composition of T-cell populations and how these may change with age.
- Define markers and functional assays that will enhance our understanding of and ability to study innate and adaptive immune function in humans, especially those approaches that permit study of the *in vivo* activity of the immune system.
- Define the reservoirs of virus in both acute and chronic infection that permit HIV persistence throughout the course of HIV infection, including in the setting of therapies and in the presence of ongoing immune responses.
- Determine the viral and host factors associated with clinical response and lack of response to therapeutic interventions in HIV infected subjects.

**To facilitate the research goals listed above:**

- Further develop and utilize experimental human, nonhuman, *ex vivo*, and theoretical/mathematical models to study the pathogenesis of lentiviral infections with emphasis on models of direct relevance to human HIV infection and models that address important issues not readily approachable in human subjects.
- Promote augmented access to and sharing of key patient samples, animal model resources, laboratory reagents, new technologies and equipment, information databases, and quantitative virologic and immunologic assays.
- Facilitate the translation of new insights from structural biology, computational biology, genomics, and proteomics to understand the immunopathogenesis of HIV infection.
- Enable the translation of basic and preclinical research findings into clinical studies in humans to advance the understanding, treatment, and prevention of HIV infection.

## OBJECTIVE–C

Define the etiology, pathophysiology, and consequences of HIV infection and treatment-related metabolic and body composition changes in diverse populations across the spectrum of age and gender in national and international settings.

(The scientific objectives C through G are of equal weight.)

## STRATEGIES

- Define the mechanisms underlying alterations in metabolism, body composition, endocrine function, growth and development, and the risks of atherosclerotic cardiovascular, vascular, and bone disease to determine:
  - ▶ the effects of antiviral therapies and suppression of virus replication;
  - ▶ the influence of disease stages;
  - ▶ the contributions of individual virologic and host factors, including genetic loci; and
  - ▶ the contributions of opportunistic infections (OIs), hormonal dysregulation, and other consequences of HIV infection.
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms underlying alterations in metabolism, body composition, growth and development, and the long-term risks of diabetes, bone disease, and atherosclerotic cardiovascular disease.
- Determine factors associated with clinical response or lack of response to therapeutic interventions against AIDS-associated metabolic and body composition changes, impaired growth and development, and the long-term risks of diabetes, bone, and atherosclerotic cardiovascular disease.

### To facilitate the research goals listed above:

- Transfer expertise from the endocrine, metabolic, cardiovascular, and bone research fields to the HIV field and promote linkage between HIV researchers and established individuals and centers of excellence in these areas of research.
- Promote programs to facilitate access to and sharing of patient samples, animal model resources, reagents, new technologies, equipment, information databases, and modeling/calculation tools used in metabolic, cardiovascular, and bone research.
- Facilitate the translation of new insights from structural biology, computational biology, genomics, and proteomics to understand the metabolic, endocrine, cardiovascular, and bone disease complications associated with HIV infection and treatment.
- Support the development of new and improved research techniques to address the emerging metabolic, endocrine, cardiovascular, and bone complications.
- Integrate metabolic, endocrine, cardiovascular, and bone studies into ongoing and planned treatment trials.
- Link advances in understanding the immune response to HIV with changes in lipid, glucose, bone metabolism, endocrine parameters, and cardiovascular disease.

## **OBJECTIVE–D**

**Elucidate the etiologic factors, cofactors, pathogenesis, and consequences of HIV-related malignancies in diverse populations across the spectrum of age and gender in national and international settings.**

**(The scientific objectives C through G are of equal weight.)**

## **STRATEGIES**

- Elucidate the fundamental immune defects in HIV infection that predispose to the development of HIV-associated malignancies.
- Identify the mechanisms by which immune dysfunction, oncogenes, suppressor genes, carcinogens, and non-HIV viral and other microbial genes and proteins contribute to the development of cancer and preneoplastic lesions in the context of HIV infection and HIV-associated malignancies; correlate these molecular factors with epidemiologic studies.
- Elucidate whether the mechanisms by which HIV-associated cancers and the same cancers that develop in HIV-seronegative individuals are shared or different.
- Identify the host factors that increase the risk of HIV-associated malignant disease.
- Determine the impact of AIDS-associated malignancies on the immune response to HIV.
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms of HIV-related malignancies, and evaluate how the manifestations of HIV-associated malignancies are altered by such therapies.
- Determine the impact of AIDS-associated malignancies on the immune response to HIV.
- Determine factors associated with clinical response and lack of response to antineoplastic therapeutic intervention in HIV infected subjects.

### **To facilitate the research goals listed above:**

- Promote programs to facilitate the development of and augmented access to *in vivo* animal models, patient specimens for HIV-associated malignancies, sharing of key patient samples, laboratory reagents, new technologies and equipment, information databases, and quantitative virologic and immunologic assays.
- Facilitate the translation of new insights from structural biology, computational biology, genomics, and proteomics to understand the etiology and pathogenesis of AIDS-related malignancies.

## OBJECTIVE-E

**Elucidate the mechanisms and consequences of HIV-associated neurological disease and neurobehavioral dysfunction in diverse populations across the spectrum of age and gender in national and international settings.**

**(The scientific objectives C through G are of equal weight.)**

## STRATEGIES

- Determine the cellular and molecular mechanisms involved in HIV-associated neurobehavioral and neurological dysfunction including:
  - ▶ identifying how HIV enters, establishes infection, spreads, and persists in the central nervous system (CNS);
  - ▶ examining the effects of HIV infection on specific cell populations and regions of the nervous system;
  - ▶ investigating the connection between blood-brain barrier dysfunction and neuronal injury in the context of HIV infection;
  - ▶ determining the relationship of virologic (including distinct subtypes of HIV), host (including the genetics of the virus/host interactions), pharmacologic, substance abuse, and environmental factors to susceptibility of neurological disease and HIV-associated neuropathogenesis (including peripheral neuropathies);
  - ▶ determining the consequences of the biological activity of cytokines, other mediators, and their receptors on the neurologic tissue in the context of HIV infection; and
  - ▶ developing methods to monitor the levels of HIV replication and consequences of HIV infection within the CNS of living subjects.
- Determine factors associated with clinical response and lack of response to therapeutic interventions for neurologic and neurobehavioral complications of HIV disease.
- Determine the host and viral factors influencing independent evolution of drug-resistant HIV strains in the CNS compartment.
- Determine the impact of HIV/CNS infection on systemic disease progression.
- Determine the role of the CNS as a reservoir of, and sanctuary for, persistent HIV infection.
- Define mechanisms of immunologic control of HIV, OIs, and coinfections in the CNS.
- Develop methods to investigate, diagnose, and monitor HIV-associated neurological and neurobehavioral disorders.
- Investigate aspects of HIV infection that uniquely influence the developing nervous system.
- Delineate the role of OIs, coinfections, other disease complications, and drug treatment in neurologic and neurobehavioral complications of AIDS including CNS dysfunction and peripheral neuropathies.
- Employ therapies that effectively suppress HIV replication to probe pathogenic mechanisms of HIV-associated neurologic diseases and neurobehavioral dysfunction; evaluate how the manifestations of HIV-associated neuropathogenesis are altered by such therapies.

**To facilitate the research goals listed above:**

- Develop and employ appropriate animal models (e.g., NHP models) of CNS HIV/SIV infection that best reflect specific aspects of the human HIV/CNS disease course on treatment that are crucial to understanding neurobehavioral and neurologic disorders.
- Ensure that information, materials, and specimens needed for neuro-AIDS research are appropriately collected, catalogued, classified, stored, and distributed, and promote access to and sharing of new technologies and equipment.
- Encourage new multidisciplinary approaches to investigate HIV-associated neurological disease and neurobehavioral dysfunction.
- Improve existing and develop new technologies for biochemical markers and the imaging of neurologic dysfunction.
- Facilitate the translation of new insights from structural biology, computational biology, genomics, and proteomics to understand HIV-related neurologic disease.
- Integrate neurologic studies into the design and conduct of treatment trials.

**OBJECTIVE–F**

Elucidate the pathogenic mechanisms and consequences of OIs and coinfections in HIV infected individuals in diverse populations across the spectrum of age and gender in national and international settings. Priority should be given to OIs and coinfections that (a) are a major cause of morbidity and/or HIV disease progression in HIV infected individuals (e.g., tuberculosis [TB]) or (b) contribute significantly to HIV transmission or acquisition (e.g., herpes simplex virus [HSV-2]).

(The scientific objectives C through G are of equal weight.)

**STRATEGIES**

- Conduct studies of the basic biology of such opportunistic pathogens and their interaction with the host.
- Identify and elucidate the genetic and environmental risk factors associated with the susceptibility to, the development of, and the progression of OIs in HIV infected individuals.
- Study the effects of OIs and coinfections on immune dysfunction and HIV disease progression.
- Define immunologic responses to OI/coinfection pathogens at mucosal surfaces and determine how they may be altered by HIV infection.
- Study how HIV infection changes the pathogenesis of the coinfecting pathogens.
- Elucidate the mechanisms of immune function that mediate protection against OIs.
- Study the effects of HIV therapy-associated immune reconstitution on the clinical course and manifestation of OIs and coinfections.
- Probe the pathogenic mechanisms of HIV-associated OIs, and evaluate how the causes, agents, and manifestations of these HIV-associated infections are altered by ART therapies.
- Define the molecular and phylogenetic characteristics of major AIDS OIs and pathogens; standardize and improve techniques of phylogenetic analysis; and integrate strain-specific characterization of data into studies of the pathogenesis, mechanisms of transmission, and epidemiology of OIs.
- Determine factors associated with clinical response and lack of response to therapeutic interventions against OIs and coinfections in HIV infected subjects.

**To facilitate the research goals listed above:**

- Facilitate the translation of new insights from structural biology, computational biology, genomics, and proteomics to understand the etiology and pathogenesis of HIV coinfections and HIV-related OIs.
- Develop *in vitro* techniques and animal models to propagate and define the life cycles of the opportunistic pathogens associated with HIV disease.
- Develop and validate diagnostic assays for the reliable and rapid identification of HIV-associated OIs, including stable, inexpensive, easy-to-perform assays appropriate for use in developing countries.

## **OBJECTIVE–G**

**Elucidate the etiology, pathogenesis, and consequences of HIV-related organ-specific disorders in diverse populations across the spectrum of age and gender in national and international settings.**

**(The scientific objectives C through G are of equal weight.)**

## **STRATEGIES**

- Investigate the etiologic and pathogenic mechanisms and consequences of HIV-related:
  - ▶ GI, including liver and biliary, diseases,
  - ▶ nephropathy,
  - ▶ endocrine dysfunction,
  - ▶ hematologic disorders,
  - ▶ pulmonary disorders,
  - ▶ autoimmune disorders,
  - ▶ cardiac and vascular disease,
  - ▶ cutaneous disease,
  - ▶ oral disease, and
  - ▶ other organ/tissue-specific disorders.
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms of HIV-related organ/tissue-specific complications, and evaluate how the manifestations of HIV-related organ/tissue-specific complications are altered by such therapies.
- Determine factors associated with clinical response and lack of response to therapeutic interventions against HIV-related disorders.
- Employ animal models to investigate the etiology and pathogenesis of HIV/SIV-associated disorders in the above systems.

### **To facilitate the research goals listed above:**

- Facilitate the translation of new insights from structural biology, computational biology, genomics, and proteomics to understand the etiology and pathogenesis of HIV-related disorders.
- Integrate studies of HIV-related disorders in the design and conduct of treatment trials.

## CHAPTER 2

# Prevention Research



**AREA OF EMPHASIS**

# Microbicides

**SCIENTIFIC OBJECTIVES AND STRATEGIES****OBJECTIVE–A**

**Elucidate basic mechanisms of HIV transmission (virus and host factors) at mucosal/epithelial surfaces that are important for microbicide research and development in diverse populations.**

**STRATEGIES****Basic Biological and Physiological Research Related to Microbicides**

- Search for and characterize new and understudied viral and host targets important for transmission and early dissemination of HIV in the female and male genital tracts and the rectal (lower gastrointestinal [GI] tract) and oral (upper GI tract) mucosal/epithelial sites that are relevant for microbicide discovery and development.
- Investigate the importance of innate and adaptive host defenses in protecting against HIV transmission and acquisition, and explore strategies to harness these host defenses to protect against HIV acquisition in the female and male genital tract.
- Determine the impact of microbicides on innate and adaptive mucosal/epithelial defense mechanisms in the female and male genital tracts.
- Study the impact of microbicides on microbial ecology and their effects on mucosal/epithelial secretions and surfaces.
- Study the physiologic changes that occur during intercourse and discern how they relate to transmission or acquisition of HIV and the safety and activity of microbicides.
- Determine the cells or tissue types that serve as portals of entry and support subsequent spread of HIV/SIV (simian immunodeficiency virus) and understand the mechanism of virus dissemination to the lymphoid tissue.
- Determine the role of viral phenotype/genotype/clade/resistance patterns in microbicide activity and delineate their relative effect on the relative efficiency of transmission of cell-free and cell-associated virus in secretions and tissues in the female and male genital tracts.
- Determine the mechanisms by which genital tract inflammation and/or infections (including sexually transmitted infections [STIs]) may influence HIV transmission and early propagation.
- Investigate the effect of endogenous hormonal states (puberty, pregnancy, menopause, lactation-induced hypoestrogenic states, and menstrual cycles) and exogenous hormonal states (including oral and injectable contraceptives and hormonal replacement therapy) on the susceptibility of the female and male genital tracts to infection with HIV.

## **OBJECTIVE–B**

**Support the discovery, development, and preclinical evaluation of topical microbicides alone and/or in combination.**

## **STRATEGIES**

### **Microbicide Development and Preclinical Studies**

- Develop, validate, and standardize specific, sensitive, and reproducible methods for assaying antiretroviral activities of microbicide candidates.
- Validate and standardize specific, sensitive, and reproducible methods for quantifying innate and adaptive responses in mucosal/epithelial tissues and secretions before and after use of microbicides.
- Develop, validate, and standardize *ex vivo* cervicovaginal and rectal explant models of human or nonhuman primate tissue that might provide a useful approach to: (1) investigate the very early events in HIV or SIV/SHIV (chimeric simian/human immunodeficiency virus) transmission and (2) evaluate the activity and toxicity of topical microbicides.
- Validate and standardize existing (nonhuman primate SIV/SHIV) microbicide efficacy and safety models, and identify and support the development of new animal models that more closely reflect the dynamics of sexual transmission of HIV in humans.
- Promote the development of new models and assays to discover and evaluate microbicide candidates, acknowledging that most assays used for microbicide development are adaptations of those used for development of systemic antivirals and may not be appropriate.
- Integrate exploratory techniques such as genomics and proteomics to identify novel candidate agents or targets for microbicide strategies.
- Facilitate access to preclinical studies of potential microbicides to assess immunologic and inflammatory effects, pharmacokinetics, pharmacodynamics, and toxicity on the mucosal/epithelial surfaces and secretions (female and male), teratogenicity, transplacental carcinogenicity, and effects on fertility.
- Investigate the effect of endogenous hormonal states (puberty, pregnancy, menopause, and menstrual cycles) and exogenous hormonal states (including oral and injectable contraceptives and hormonal replacement therapy) on the safety and efficacy of microbicides.
- Foster methods designed to solve manufacturing and synthesis hurdles that may prevent the advancement of microbicides through the preclinical pathway, by providing support for early Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP) manufacturing design and scale-up.

## OBJECTIVE–C

**Develop and assess acceptable formulations and modes of delivery for microbicides, bridging knowledge and applications from the chemical, pharmaceutical, physical, bioengineering, and social sciences.**

## STRATEGIES

### Microbicide Formulations and Modes of Delivery

- Develop formulations, dosage, and delivery systems suitable for the genital and GI tracts, so that toxicity and trauma to the tissue are reduced or eliminated.
- Develop formulations that share the same physical and chemical properties of the microbicide formulation but lack antimicrobial activity and toxicity, to serve as placebos.
- Identify and validate methods that improve the understanding of bioadhesion, biodispersion, retention, and distribution of microbicide formulations prior to, during, and after intercourse.
- Develop methods to measure tissue and systemic absorption following topical microbicide use.
- Develop and incorporate culturally sensitive measures and mechanisms to assess microbicide and delivery mode acceptability in diverse populations of men and women that are and may be used in exploratory clinical studies as well as phased clinical trials.
- Understand the biologic mechanisms and physiologic changes that contribute to efficacy and safety of microbicide formulations, including, but not limited to, hormonal status, age, menstrual cycle, nature of intercourse, pregnancy, frequency of use, sexual arousal, and concomitant STIs.
- Develop, validate, and standardize methodologies to analyze the physical and chemical properties of individual microbicides, formulated microbicides, and combinations of microbicides.
- Develop methodology and supportive studies to evaluate product characteristics of microbicides (such as taste, smell, color, lubricity, and texture) that may affect acceptability and adoption/use of microbicides in diverse populations and for different types of sexual acts.
- Promote the application of the new sustained-release and solid-phase formulations technology for the development of microbicides that will enable product use independent of coitus.
- Support the development of reference formulations with known acceptability profiles that can be used as a starting point for optimization of microbicide delivery.

## **OBJECTIVE-D**

**Conduct clinical studies of candidate microbicides to assess safety, acceptability, and effectiveness in reducing sexual transmission of HIV in diverse populations in domestic and international settings.**

## **STRATEGIES**

### **Clinical Trials of Microbicide Products**

- Develop and evaluate improved culturally informed methods to recruit and retain participants for Phase I, II, and III microbicide studies at domestic and international sites.
- Conduct research on mechanisms to improve clinical trial adherence and compliance with use requirements of products under study.
- Identify, develop, and validate behavioral and biological markers to evaluate safety, effectiveness, and adherence to microbicides, including designing, developing, and evaluating tools to measure product use and acceptability both within and outside the clinical trial environment.
- Address ethical issues in the design and conduct of microbicide trials, including how to optimize informed consent among participants.
- Conduct research on the acceptability and effectiveness of microbicides relative to and in combination with other behavioral, preventive, and therapeutic methods.
- Identify and develop improved relevant techniques to evaluate safety of microbicides when applied to genital mucosal/epithelial surfaces during clinical trials.
- Follow up seroconverters in clinical trials to assess the impact of long-term product use and to assess the specific effect of these products on other STIs, contraception, and pregnancy.
- Enhance understanding of the significance of clinical findings identified by current methods to evaluate safety, including evaluation of cervicovaginal, anorectal, and penile irritation.
- Study microbicide products in HIV infected people under treatment to determine their impact on the development of drug resistance, drug-to-drug interactions, and the potential for other adverse events.
- Design, implement, and evaluate Phase IV postmarketing surveillance studies once an effective and safe microbicide has been identified in Phase III trials.

**OBJECTIVE-E**

**Conduct basic and applied behavioral and social science research to inform and optimize microbicide development, testing, acceptability, and use domestically and internationally.**

**STRATEGIES****Social Science Research Related to Microbicides**

- Support theory-building and the development of behavior epidemiological models of risk and protection in the context of microbicide research, development, and rollout.
- Conduct research on how microbicide use affects and is affected by psychological and social factors, incorporating a developmental perspective on individual, partner, and social influences.
- Develop and evaluate the efficacy of behavioral interventions to enhance correct and consistent use of microbicide products in diverse populations in different settings.
- Support health services/operations research on the implementation and costs of interventions using microbicides, including studies of dissemination, sustainability, acceptance, and adoption of microbicide interventions by health care providers.
- Improve methods and develop focused new and improved tools for microbicide research, including enhancing survey methods and tools, collecting valid self-report data, collecting behavioral and disease outcomes, measuring change over time, and recruiting and retaining subjects in clinical trials.
- Conduct research on optimal counseling approaches to enhance health decisionmaking around partially efficacious microbicides and the implications for HIV prevention.

## **OBJECTIVE–F**

**Establish and maintain the appropriate infrastructure (including training) needed to conduct microbicide research domestically and internationally.**

## **STRATEGIES**

### **Infrastructure**

- Establish clinical trial sites and the infrastructure required for Phase I, II, and III studies domestically and internationally, and coordinate with efforts of other organizations to optimize available resources and encourage harmonization.
- Identify site-specific gaps in biomedical, behavioral, ethical, clinical, regulatory, and administrative training in national and international microbicide research sites, and design strategies that respond to these needs.
- Provide microbicide research training activities to foster and develop the acumen of national and international independent investigators (including development of mentor relationships and grant and protocol writing skills).
- Foster the dissemination of microbicide-related discovery and development strategies, including assay standardization and validation, to international investigators.
- Strengthen training and infrastructure for the development of national and international institutional capacity for microbicide research, including the enhancement of laboratory capability, data management/analysis, population-based research, high standards of conduct for clinical research, operational support, and physical infrastructure.
- Ensure the involvement of national and international communities in the planning and undertaking of international microbicide research.
- Foster and support the development of pilot and large-scale GMP production systems for the manufacture of microbicide active agents and their formulations.
- Develop strategies to promote the involvement of local governments, communities, and advocacy groups in the identification of priorities for and development of clinical protocols, and to sustain these efforts during the conduct of clinical trials.
- Foster interactions in the form of public and private partnerships aimed at integration of NIH microbicide activities with external organizations to accelerate microbicide development.

**AREA OF EMPHASIS**

# Vaccines

**SCIENTIFIC OBJECTIVES AND STRATEGIES****OBJECTIVE–A**

**Increase scientific knowledge through basic research on protective immune responses and host defenses against HIV to facilitate the development of vaccines and other biomedical intervention strategies to prevent and/or control HIV infection.**

**STRATEGIES**

- Define the mechanisms underlying protective systemic and mucosal immunity to HIV and other closely related lentiviruses by pursuing research in models that will provide information directly relevant to HIV infections; this includes the following areas of interest:
  - ▶ Determine the mechanisms of immunologically mediated control of infection with HIV and other related lentiviruses, including the role of antigen-specific (adaptive) and antigen-nonspecific (innate) cellular and humoral immunity in inhibiting viral replication to provide a basis for optimal vaccine design.
  - ▶ Define the structure-function relationships and the antigenicity and immunogenicity of HIV envelope proteins, including transient or intermediate and conformational domains induced by virus interacting with CD4, chemokine, dendritic cell (DC) surface proteins and adhesion molecules, and other cellular receptors to improve vaccine designs to more effectively induce immune responses to block infection by active T-cell immunity and protective antibody.
  - ▶ Define and characterize viral B-cell and T-cell epitopes that induce protective immunity in HIV or AIDS-related disease; utilize structural analysis of envelope to determine whether and how their immunogenicity can be improved and exploited in vaccine development.
    - Determine the mechanism of how HIV and closely related lentiviruses evade or escape from humoral and cellular immune responses; design vaccine approaches to prevent this; and define conserved epitopes in which genetic substitutions cannot be tolerated by the virus.
    - Characterize pathways of antigen processing of HIV proteins, including envelope glycoproteins, for presentation by major histocompatibility complex (MHC) class I and class II molecules. Investigate the interaction of HIV proteins with antigen-processing mechanisms that enhance or inhibit specific epitope presentation to the immune system.
    - Study the role of DCs in the induction of immunological memory and long-term protective function of different subsets of human lymphocytes in HIV-related disease and in response to vaccination.
    - Define factors that favor establishment and maintenance of memory cells able to generate effective recall to vaccine antigens, particularly HIV and viral antigens of closely related lentiviruses, and development of long-term protective immunity, particularly in human subjects.

- Study the mechanism of action of vaccine adjuvants for HIV immunogens that enhance HIV/SIV (simian immunodeficiency virus) antigen presentation to induce different cytokine or chemokine responses, innate immunity, and host factors; carry out comparative translational research in nonhuman primate (NHP) and human vaccines.
- Determine how chronic infection with one strain of HIV or closely related lentivirus, including attenuated viruses, confers protection against subsequent infection or reduces viral replication of a second pathogenic virus strain. Define the properties of the virus and of the immune responses that are responsible for lack of disease induction by attenuated viruses and/or protection from challenge with related pathogenic virus, and determine the protective mechanism, duration, and extent of cross-protection.
- Define the heterogeneity of specific responses to vaccine immunogens, specifically those derived from HIV, SIV, and SHIV (chimeric simian/human immunodeficiency virus), within diverse tissue compartments, and identify factors that confer protection from infection by various routes including vaginal, rectal, oral, and parenteral exposure.
- Determine which factors promote development of particular human anti-HIV effector cell types, promote production of antiviral substances including chemokines, or enhance non-antigen-specific innate protective mechanisms.
- Define the basis for adaptive, antigen-specific immune reactivity (humoral, cellular, and other) across divergent HIV types (clades and biological phenotypes or immunotypes); study clinical samples from human volunteers participating in HIV vaccine trials to determine the extent of cross-reactive immune responses that can be achieved with different candidate vaccines.
- Determine whether HIV immune responses that can contribute to immune enhancement of viral replication *in vitro* can interfere with induction or propagation of vaccine-induced effector responses *in vivo*.
- Seek new clues for correlates of immune protection and vaccine design by studying HIV infected or highly exposed but seronegative individuals, across the lifespan, and SIV or SHIV NHP lentivirus models by conducting the following research:
  - ▶ Study acutely HIV infected individuals, exposed/seronegative, or possibly transiently infected humans (including uninfected children born to HIV infected mothers, individuals with controlled therapy interruptions, HIV infected individuals vaccinated with therapeutic vaccines while on antiviral therapy, and nonprogressors) to define immune responses to HIV-1 and HIV-2, potential vaccine-inducible host immune responses, and viral factors (or viral attenuations) that reduce the amounts of circulating virus and influence disease course.
  - ▶ Elucidate the functional mechanisms for protective immunity against HIV, SIV, and SHIV, including identification of specific responses by passive transfer of antibody or immune cells and deletion of selected immune subsets in NHP models.
  - ▶ Investigate the sequence of events required for mucosal transmission/infection of HIV, SIV, or SHIV at different portals of entry to define how and where specific immune effector mechanisms can impede viral entry and/or prevent establishment of infection.
  - ▶ Study mucosal immunity to HIV and SIV antigens and other infectious pathogens being used as HIV vaccine vectors in relevant animal models and humans to develop optimal vaccine strategies for HIV antigen delivery and effective immune-based prevention of HIV transmission.
  - ▶ Acquire clinical specimens from populations relevant to HIV vaccine trials for laboratory studies; explore the molecular epidemiology, humoral, and cell-mediated immune responses to HIV-1 and their relationship to

class I and class II MHC alleles; and define constraints on HIV evolution under immune selection pressure so as to guide vaccine development. Acquire appropriate, linked, epidemiological information to optimize interpretation of these analyses.

- ▶ Monitor the effects on immune activation with intercurrent sexually transmitted diseases (STDs), malaria, tuberculosis (TB), hepatitis B and C, human papillomavirus (HPV), and other infectious diseases, and with administration of drugs of abuse or effects of antiretroviral therapy (ART) on HIV shedding in vaccinated subjects. Model these confounding elements in NHP.
- Develop *in vitro* experimental approaches for analysis of HIV vaccine responses that will combine sensitivity, specificity, high throughput, and the ability to use small sample volumes; develop *in vitro* and *in vivo* tools to study systemic and mucosal immune mechanisms of control of virus for analysis of vaccinated individuals (across lifespan) and animals protected against SIV or SHIV by undertaking the following research activities:
  - ▶ Develop and improve NHP animal models of lentivirus infection that are practical and representative of the spectrum of HIV infections and development of AIDS, including use of appropriate HIV cellular receptors and different modes of transmission; develop genetically defined and histocompatible NHP models to facilitate immune cell transfer studies; in general, make models amenable to use in evaluating protection by vaccines and other biomedical interventions. This may be approached, in part, by a genetic sequencing, particularly of selected regions of the macaque genome.
  - ▶ Develop improved methodologies and assays to measure HIV neutralization; explore the mechanisms of virus neutralization and the reason(s) for the relative difficulty to neutralize primary HIV isolates.
  - ▶ Develop and standardize immunological reagents for HIV vaccine trials; standardize cell, fluid, and tissue processing to ensure viability and maintenance of functional capacity of cells and stability of factors in serum, plasma, and culture supernatants; and develop quality control procedures for collecting, processing, freezing, storage, recovery, viability, shipping, and tracking of samples that will be essential in large-scale HIV vaccine trials.
  - ▶ Study the function of HIV/SIV-specific CD4 T cells, CD8 T cells, and viral suppressive immune responses; develop and adapt high-throughput assays with specificity for primary HIV isolates; and make available those reagents required for HIV vaccine-related studies.
  - ▶ Develop or improve sensitive quantitative measures of HIV (and SIV) in body fluids and low-level tissue reservoirs, including genital secretions and breast milk, to assess the effectiveness of vaccines designed to lower viral load and interrupt transmission or prevent disease progression.

## OBJECTIVE-B

Design HIV antigens, adjuvants, immunomodulators, and vaccine delivery methods that elicit long-lasting protective immune responses against a broad range of HIV isolates by applying findings from basic, epidemiologic, and clinical research; facilitate development and preclinical evaluation of vaccine strategies in laboratory studies and animal models; and foster early and continued collaboration between academicians, other Government agencies, nongovernmental organizations (NGOs), and industry in the research and development of candidate vaccines to test a broad array of vaccine concepts and combinations of different approaches for development of potential HIV vaccine products, including vaccines for particular populations.

## STRATEGIES

- Multiple parallel approaches to development and testing of candidate HIV/AIDS vaccines will be investigated to provide complementary and comparative preclinical data on safety and immunogenicity questions about HIV vaccines. Such studies should achieve the following:
  - ▶ Support the design, development, production, and testing of novel HIV/AIDS vaccine candidates for safety and for their ability to elicit appropriate antiviral immune responses. This may include, but is not limited to:
    - Virus-like particles containing one or more virus proteins, peptides, or antigens;
    - Whole-inactivated HIV rendered noninfectious by chemical and/or genetically engineered deletions of pathogenic viral elements;
    - Naturally occurring and genetically engineered, live-attenuated strains of HIV;
    - DNA or RNA coding for viral proteins;
    - Live, recombinant viral and bacterial vectors engineered to express one or more HIV proteins with attention to vectors that might provide dual benefit for HIV and some other pathogen or to vaccine vectors that target mucosal immune responses;
    - Viral replicons or other strategies to target DCs;
    - Recombinant HIV envelope protein subunits produced by a variety of methods, with an emphasis on retention or exposure (e.g., through deglycosylation) of critical nonlinear or conformational structural epitopes for induction of effective antibody responses;
    - Structurally constrained HIV envelope fragments, peptides, mimetopes, or complex peptides capable of inducing and boosting cellular or humoral immunity to HIV; and
    - Cell surface components carried on the viral surface.
- Foster collaboration between academic investigators, industry sponsors, the NIH, the Food and Drug Administration (FDA), other Government agencies, and NGOs on research and development of novel vaccine design concepts. These collaborations should:
  - ▶ Enable production of pilot lots of HIV vaccine candidates for testing in NHPs and human subjects. Where necessary, the NIH will provide products produced under clinical grade Good Manufacturing Practices (cGMP) and ensure that products meet these standards;

- ▶ Develop programs to design and conduct comparative testing of vaccine approaches with industry and academic partners that will permit long-term followup to assess disease progression in animal models; and
- ▶ Develop infrastructure; address scientific, legal, ethical, and regulatory issues to foster and encourage participation by, and collaboration among, academic investigators, industry, affected communities and populations, and other agencies in the research, development, production, and clinical testing of candidate vaccines.
- Foster the development of HIV vaccines to optimize characteristics appropriate for broad international use, including designs exhibiting low cost with ease of production, stability, and ease of administration. This may include:
  - ▶ Combined use of two or more vaccine strategies with mixed modalities to boost the same component and/or to engage different arms of the immune response; and
  - ▶ Multivalent vaccine candidates incorporating different genetic clades and/or antigenic types to increase the breadth of immune responses.
- Support HIV vaccine design and development, incorporating methods to improve or modulate vaccine-elicited immune responses (qualitatively or quantitatively), including:
  - ▶ Novel adjuvants and delivery methods that might enhance effective DC presentation of HIV/SIV antigens;
  - ▶ Agents that stimulate or modulate mucosal immune responses to HIV or other host defenses, including cytokines or chemokines;
  - ▶ HIV/SIV vaccines formulated with cytokines or incorporating cytokine genes or other biologically active molecules in vectors; and
  - ▶ Other novel strategies, including nutritional supplementation and treatment of underlying infections and/or diseases that might have an impact on HIV vaccine responses.
- Evaluate the efficacy of HIV/SIV vaccine and other immune prevention strategies in NHP animal models of HIV and closely related lentiviruses by:
  - ▶ Testing HIV/SIV vaccine and other biomedical prevention strategies in animal models that most closely mimic HIV infection in humans;
  - ▶ Determining *in vitro* correlates of an *in vivo* protective immune response generated by HIV/SIV vaccines;
  - ▶ Determining the effect of HIV/SIV vaccine formulation, site of delivery, and regimen, as well as the nature, timing, phenotype, and route of infectious SIV or SHIV challenge on the effectiveness of the vaccine-induced immunity;
  - ▶ Defining the impact of different HIV/SIV vaccine approaches on the kinetics of immune responses, kinetics and localization of viral replication, including long-term followup of disease progression in the presence of low-level chronic infection and concomitant diseases (e.g., TB, hepatitis, or autoimmune diseases), and biologic characteristics of breakthrough virus including transmissibility;
  - ▶ Determining the impact of genetic factors and age on HIV/SIV vaccine responses and on protection against virus at various challenge sites; and
  - ▶ Studying the efficacy of the HIV/SIV immune response in the face of viral mutation and variation.

- Investigate HIV/SIV vaccines and other biomedical prevention strategies with attention to potential factors such as integrity of the mucosal surface, changes in vaginal/cervical epithelium during puberty, hormonal changes during pregnancy, use of contraceptives or hormone replacement therapy, and presence of STDs; wherever possible, study potential concomitant effects on the genital tract immune responses and how inflammatory activity might compromise integrity of the mucosal surface or the inductive ability of HIV vaccines.
- Support development of reagents and standardized methods to assess specific HIV or SIV vaccine-induced immune responses in NHP animal models and humans, including infants, for both humoral and cellular aspects of systemic and mucosal immunity. This includes:
  - ▶ Developing and refining assays to distinguish between serological and cellular responses due to immunization versus those due to HIV, SIV, or SHIV infection;
  - ▶ Characterizing and evaluating potential negative side effects of candidate HIV/SIV vaccine designs, including the potential to increase the susceptibility to infection or the rate of disease progression in NHP animal models;
  - ▶ Standardizing and validating assays to assess potency of candidate HIV vaccines;
  - ▶ Standardizing and validating assays to be used as Phase III study endpoints; and
  - ▶ Abiding by Good Laboratory Practice (GLP) regulations to perform endpoint assays in support of product licensure and instituting quality assurance programs to assure sponsors and vaccine manufacturers that the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with regulations stated in 21 CFR Part 58 and Part 11.
- Foster research on the safety and regulatory considerations of candidate HIV/AIDS vaccines in development:
  - ▶ Whose production utilizes human-derived tumor cell and other continuous cell lines;
  - ▶ That utilize vectors that have the potential to integrate into the host chromosome or have the potential for chronic expression;
  - ▶ That might have the ability to be generated as either replicating or nonreplicating vectors;
  - ▶ That have the potential to cause autoimmunity or highly immunogenic antivector responses; or
  - ▶ That overexpress potentially harmful vector proteins.

## OBJECTIVE–C

**Identify mechanisms of protective immunity to HIV in newborns and infants, and support the development of distinct study designs for safe and effective vaccine strategies and passive immune interventions, alone or in combination with other interventions, for preventing or controlling HIV infection in this population worldwide.**

## STRATEGIES

- Investigate the unique immune status and develop immune interventions in both pregnant women and infants to interrupt HIV transmission. Active and passive HIV vaccine strategies need to be modeled and evaluated, particularly in infants, in parallel to studies in uninfected adults. To accomplish this goal, it is important to develop research that will achieve the following:
  - ▶ Develop relevant NHP animal models of maternal-fetal and maternal-infant perinatal transmission of HIV/SIV/SHIV that can:
    - Determine preclinical safety and immunogenicity of various HIV vaccines and adjuvants, particularly in pregnant and newborn primates;
    - Determine safety of various monoclonal and polyclonal antibody preparations against HIV;
    - Determine the best immunization routes or protocols to induce antibodies to HIV in milk and other secretions;
    - Evaluate efficacy of vaccines and passive immunotherapy for prevention of perinatal or breastfeeding HIV transmission; determine whether there is attenuation of disease progression among neonatal animals that become infected despite immune intervention; determine correlates of protective immunity; and
    - Evaluate the effect of ART in combination with immune and behavioral prevention strategies.
  - ▶ Determine virologic and nonimmunologic/genetic host factors that influence transmission of HIV-1 from mother to infant that would have an impact on selection of viral antigens for the design of an HIV vaccine or for identifying the target of immune-based intervention to prevent perinatal transmission. This includes:
    - Determining the importance of viral load and viral phenotypes and genotypes in perinatal or early infant HIV transmission and what additional viral factors are associated with differences in perinatal transmissibility;
    - Developing standardized methods to collect specimens and to detect, characterize, and quantify HIV in cervicovaginal secretions and in breast milk to determine their potential relevance in mother-to-child transmission (MTCT); and
    - Determining if HIV in maternal genital secretions or breast milk is distinguishable from virus found in blood and which type is transmitted from mother to fetus and mother to infant.
  - ▶ Identify maternal and infant immune responses that might control HIV replication in either the mother and/or the infant and prevent transmission of HIV or establishment of infection in infants.
- Define immune approaches that will provide specific and sustained protection against HIV/SIV transmission; develop the products necessary to achieve these goals; and develop the capacity to evaluate their safety in human subjects. This research includes the following activities:

- ▶ Determine specific immune strategies for perinatal intervention that blocks interaction of HIV/SIV with its receptors and coreceptors and/or that targets infected cells.
- ▶ Characterize the transmitted viral strains and monitor changes that may occur in proposed HIV vaccine trial sites; evaluate the impact that genetic polymorphism in different racial or ethnic backgrounds might have on receptor usage or immune responsiveness.
- ▶ Evaluate, in Phase I and Phase II studies, the safety and immunogenicity of various HIV vaccines, adjuvants, vaccine administration regimens, and the pharmacokinetics of passive antibody preparations among both HIV infected pregnant women and newborns exposed to HIV (born to HIV infected women).
- Test the safety and efficacy of active and passive HIV vaccine interventions alone or in combination with other modes of intervention, particularly in international settings with high seroprevalence. This testing includes the following activities:
  - ▶ Identify and characterize the important issues to consider in the development of criteria for advancement of candidate HIV vaccines, adjuvants, and passive antibody preparations from Phase I and Phase II to Phase III clinical trials in pregnant HIV infected women and/or HIV-exposed children. These criteria may include evidence of therapeutic effectiveness in mothers in addition to prevention of infection in HIV-exposed children.
  - ▶ Develop the capacity in domestic and foreign trial sites necessary to enroll mothers and infants in trials of both preventive and therapeutic HIV vaccines, passive immunity, and other perinatal interventions with prospective long-term followup. For vaccines, this should include the assessment both of duration and breadth of detectable humoral immune responses and of memory or recall responses in the cellular immunity compartment(s).
  - ▶ Conduct Phase III clinical trials for evaluation of efficacy of the most promising candidate HIV vaccines and/or passive antibody preparations that meet established criteria in pregnant HIV infected women and/or children exposed to HIV.
  - ▶ Develop criteria to define infant HIV infection status as a perinatal intervention trial endpoint in countries where breastfeeding is recommended despite maternal infection status, including type of diagnostic tests, timing of the tests, length of followup, and adherence to followup visits.
  - ▶ Study HIV isolates and the immune response in infants who become infected despite administration of active and/or passive immunization to evaluate the effects of immune intervention on the characteristics of transmitted (escape) virus and on the quality, quantity, and timing of the infected infant's antiviral responses.
  - ▶ Study the impact of early ART interventions and HIV vaccines given while on effective ART, on the maintenance or regeneration of antiviral immune responses in HIV infected infants.

## OBJECTIVE-D

**Conduct Phase I, Phase II, and Phase III trials for safety, immunogenicity, and efficacy with suitable candidate HIV vaccines or concepts in domestic and international settings.**

## STRATEGIES

- Support the conduct of Phase I, II, and III HIV vaccine clinical trials that will determine long-term and short-term safety, evaluate efficacy, and compare immunologic responses to different preventive vaccine candidates by evaluating a broad range of humoral, cell-mediated, and mucosal immune parameters. This includes the following:
  - ▶ Design and conduct Phase I and Phase II trials using promising HIV vaccine candidates. Trials should determine safety, test immunogenicity of vaccine concepts, and address questions about optimal vaccine strain selection (i.e., the properties of a strain [immunologic, genotypic, or phenotypic]) that make it optimal for use in a selected population. Trials also should include an appropriate representation of the general populations (gender, age, ethnic and racial minority) and populations affected by HIV, and be of an appropriate size to provide data on the frequency, magnitude, and breadth of immune responses to facilitate decisions regarding initiation and evaluation of larger proof-of-concept or efficacy trials.
- Develop a comprehensive plan for conducting HIV vaccine trials with a high level of retention and adequate followup of vaccinees to reach predefined endpoints, as follows:
  - ▶ Prepare for adequate long-term followup of volunteers in HIV vaccine clinical trials to determine the durability of immune responses and protection, the correlates of immune protection, long-term safety, behavioral factors to influence adherence of followup visits, the impact of participation on risk-taking behavior, and vaccine-related reduction (or enhancement) of disease progression and HIV transmission.
  - ▶ Conduct collaborative large-scale efficacy trials of preventive HIV vaccine candidates that have proven promising, safe, and immunogenic in Phase II trials and that meet appropriate criteria by:
    - Evaluating HIV vaccine candidate efficacy against HIV infection, disease progression, and/or transmission;
    - Evaluating additional virologic, immunologic, and behavioral outcomes, particularly potential correlates of protective immunity against HIV;
    - Ensuring that HIV vaccine trials are conducted with the highest regard for social, legal, and ethical standards and in populations that reflect the racial and ethnic burden of the HIV disease;
    - Ensuring access to achievable, sustainable, and culturally appropriate best practices to prevent HIV exposure; and
    - Developing, adapting/modifying, and coordinating educational and information programs about HIV and HIV vaccines suitable for the individual participants and communities of different ethnic, racial, and cultural backgrounds that will be involved in trials.
  - ▶ Characterize the clinical course, immune responses, and other characteristics of vaccinees (e.g., behavioral risk of infection) who become HIV infected; isolate and characterize viral isolates from participants in vaccine trials with intercurrent HIV infections to explore the possible effects of vaccination on the characteristics of escape (transmitted) viruses.

- ▶ Continue to use existing strategies to avert social harm and develop additional strategies to complement existing mechanisms at the local and national levels to reduce the risk of social and economic harm to volunteers in Phase I, II, and III HIV vaccine trials and assist in providing solutions.
- ▶ Conduct behavioral risk assessment research during HIV vaccine trials, particularly with Phase II and Phase III trial participants, to identify and evaluate any changes in risk behavior as a result of participation in an HIV vaccine trial; develop, test, and ensure access to interventions to prevent high-risk behaviors; conduct behavioral research with specific emphasis on individuals who become infected during trials to identify interventions that may prevent high-risk behaviors in future trials or application of HIV vaccines.
- ▶ Closely coordinate the evaluation of research findings on prophylactic HIV/AIDS vaccines with preclinical vaccine research and HIV immunotherapeutic interventions.

## OBJECTIVE-E

**Develop strategies, infrastructure, and collaborations with researchers, communities, other U.S. Government agencies, other Governments, international and domestic NGOs, and industry that are necessary to ensure adequate performance of HIV vaccine trials, while balancing the prevention needs of the at-risk populations; identify domestic and foreign populations; and perform necessary research to define seroincidence and viral subtypes and to determine and optimize feasibility of vaccine studies in appropriate cohorts.**

## STRATEGIES

- Identify and develop potential domestic and foreign sites with a high HIV seroincidence and improve access to populations at high risk for acquiring HIV infection, where vaccine or other prevention research activities may be feasible. This includes the following activities:
  - ▶ Track the course of the epidemic by applying newer epidemiologic tools for estimating the HIV incidence in various populations with documented high-risk behaviors in the United States and worldwide; improve methods to identify and evaluate emerging risk groups and those groups most likely to be informed, willing, and able participants in HIV vaccine trials.
  - ▶ Identify and address barriers to participation in clinical trials among all at-risk groups, so that all relevant populations, especially women and adolescents, are included in HIV vaccine trials.
  - ▶ Develop new laboratory diagnostic tools that can be adapted for high throughput to study new HIV infections and allow distinction between vaccinees and infected individuals.
  - ▶ Analyze MHC genetic differences and other relevant genetic or medical factors of populations at potential trial sites that might affect the qualitative or quantitative levels of immune responses to candidate HIV vaccines, susceptibility to infection, control of viral load, and disease progression.
  - ▶ Acquire and analyze HIV isolates from mucosal sites, as well as blood from recently infected people representative of potential efficacy trial populations, so that genetic and antigenic information about viruses being transmitted in the population can be obtained.
  - ▶ Develop and maintain the necessary immunology and virology laboratory infrastructure for conducting domestic and international HIV vaccine efficacy trials. This includes education and training of personnel from international sites hosting vaccine trials; development of laboratory infrastructure; standardization of assays and development of panels of geographic-specific reagents composed of local, indigenous HIV+ and HIV- samples as well as peptide reagents to serve as controls when validating and standardizing assays that will be used in support of clinical trials in that region; and participation of trained personnel in studies related to the trial.
- Establish, build, and nurture linkages with communities and community organizations where vaccine trials might be conducted to optimize education, recruitment, and followup activities; listen to and address community concerns and social issues, and ensure ethical conduct of HIV/AIDS vaccine efficacy trials. This includes the following:
  - ▶ For all HIV vaccine trials, enlist participation of local representatives or community advisory boards (CABs) in the development of appropriate trial protocols as well as responsive mechanisms to inform and educate the participating individuals; establish networks within the community that will effectively, and on a continuing basis, address the social and medical concerns of the participants; establish mechanisms to provide ongoing information and open discussions concerning the scientific rationale and public health need for the study.

- ▶ Develop mechanisms through CABs to engage collaboration and to provide education and the means to inform communities about HIV vaccines on a continuing basis so that social as well as medical concerns are addressed; work to establish trust in the community through open discussions of scientific rationale, expectations, and concerns.
- ▶ For international trials, in addition, work closely with national (host) governmental and regulatory authorities, collaborating institutions or agencies, local community representatives, vaccine manufacturer(s), and the World Health Organization (WHO)/Joint United Nations Programme on HIV/AIDS (UNAIDS) to prepare for, plan, and conduct HIV vaccine trials adhering to the highest ethical and scientific standards.
- In collaboration with Government agencies, institutions, NGOs, and communities being identified as potential collaborators, explore behavioral and social issues and prevention activities that might have a substantial impact on either the design or the conduct of an HIV vaccine trial. This includes the following research:
  - ▶ Evaluate other biomedical and behavioral interventions that could prove of benefit in decreasing the incidence of HIV infection in the populations identified for future vaccine efficacy trials; address their potential impact on the evaluation of HIV vaccine efficacy.
  - ▶ Conduct behavioral research in populations at high risk for HIV infection to determine, for example, appropriate risk-reduction interventions and to estimate risk behavior and recruitment, adherence, unblinding, and retention strategies pertinent to the design and execution of a successful vaccine efficacy trial, especially for populations that have been historically underrepresented in clinical trials and where the HIV epidemic is expanding disproportionately.
  - ▶ Identify and develop strategies to involve the populations with highest risk for HIV transmission in different communities; particular attention should be given to adolescents and young persons who are engaging in high-risk behaviors.
  - ▶ Develop research that anticipates and addresses effectively the potential adverse or unintentional effects of biomedical advances in HIV prevention (e.g., vaccines, microbicides, rapid testing, etc.), including behavioral disinhibition or increases in risk behavior such as failure to use condoms in sexual encounters, which may offset gains in prevention.
  - ▶ Collaborate with other U.S. Department of Health and Human Services (DHHS) agencies and community-based organizations to develop education programs to facilitate the conduct of Phase III HIV vaccine trials in hard-to-reach populations in domestic sites; collaborate with the U.S. Military HIV Research Program (USMHRP), the Centers for Disease Control and Prevention (CDC), the U.S. Agency for International Development (USAID), and other organizations to develop vaccine trial sites in international settings.
  - ▶ Evaluate the impact of community-based participatory research in the acceptability of HIV vaccine trials.
  - ▶ Develop appropriate communication strategies involving affected communities in the process of testing HIV vaccines and prepare for the eventual integration of preventive vaccines into comprehensive prevention and care programs in the United States and in countries where HIV vaccine trials are conducted.
  - ▶ Determine possible adverse social, economic, behavioral, or legal consequences of participation in clinical trials; develop broadly applicable strategies for mitigating potential harm.
  - ▶ Determine optimal methods of achieving informed consent for HIV vaccine efficacy trials.
- Explore innovative trial designs to improve efficiency of HIV vaccine efficacy studies (e.g., determine the impact of HIV vaccines on subsequent transmission from vaccinated individuals who become infected after administra-

tion of the trial vaccine or utilizing initially concordant HIV-negative couples at high risk or discordant couples). This includes the following areas of trial design research:

- ▶ Consider the use of secondary endpoints, particularly immune correlates of protection, surrogates of disease progression and clinical outcomes, and the benefit of long-term followup.
- ▶ Consider the impact of early ART on HIV infections in complex trial designs.
- ▶ Encourage linkage between vaccine preparedness studies in high-risk populations and other research activities, including research on TB and STDs.



**AREA OF EMPHASIS**

# Behavioral and Social Science

**SCIENTIFIC OBJECTIVES AND STRATEGIES****OBJECTIVE–A**

Develop, evaluate, and advance prevention interventions: Support research to develop, evaluate, and diffuse effective behavioral, social, environmental, and economic interventions to prevent HIV transmission and acquisition by reducing HIV-related risk behaviors and increasing protective behaviors, including studies of “scaling up” effective interventions. Both domestic and international interventions should address the social and cultural contexts within which risks occur (e.g., social class, gender, race, age, education, and ethnicity) and attend to ethical issues.

**STRATEGIES**

- Develop and evaluate the efficacy, effectiveness, and cost-effectiveness of demographically and culturally appropriate behavioral and social interventions in different domestic and international settings and populations to reduce high-risk HIV-related sexual and drug-use behaviors and HIV transmission.
- Translate and apply basic behavioral and social science research to optimize the development of innovative and effective intervention strategies.
- Support new research to characterize the active ingredients of efficacious, theory-based interventions for broader adaptation and uptake.

**Populations and Contexts**

- Develop and test interventions targeted at HIV infected persons to reduce their risky sexual and drug-use behaviors.
- Support intervention research that addresses the impact of alcohol and/or drugs on sexual encounters that may contribute to HIV transmission and acquisition.
- Continue development of interventions targeting at-risk populations (e.g., injection drug users [IDUs], other drug users, partners of drug users, street children, and men who have sex with men [MSM]), with particular emphasis on drug-use and sex-related risks.
- Continue development of interventions for persons with multiple mental and physical disorders.
- Support domestic and international intervention research on the HIV prevention role of programs designed to enhance healthy sexual development and protective behaviors (including avoidance of too-early or nonconsensual sex, abstinence from unsafe sexual behavior, and access to and use of barrier methods) throughout one’s lifetime.
- Support interventions for populations that are currently at low risk or that perceive themselves to be at low risk for HIV infection, but that may be susceptible to engaging in high-risk behaviors (e.g., non-sexually active,

non-drug-using adolescents; subpopulations of heterosexual men and women; and certain middle-aged and older populations).

- Support intervention research that addresses important contextual risk factors for disproportionately affected groups that continue to demonstrate high-risk behaviors. This research also should identify which public health applications most effectively attend to cultural contexts.
- Develop, test, and evaluate interventions that target individuals both within prisons and returning to society from the prison system; strategies include increasing access to education, information, therapeutic care, substance abuse treatment, prevention services, and clinical trials.
- Support the capacity to develop rapidly domestic and international intervention studies in response to changes in the epidemic.

### **Effectiveness**

- Develop, test, and evaluate interventions that target a range or combination of levels of social organization (i.e., individual, dyad, family, network, community, institution, and society) and that examine how these levels interact to affect HIV risk and protective behavior and HIV transmission in different cultural contexts.
- Support research to increase the effectiveness of family planning interventions and treatments for drug abuse, mental disorder, and alcohol abuse as strategies of HIV prevention.
- Conduct studies to identify key components of efficacious interventions to facilitate transfer, adaptation, and application of them.
- Support research in the United States and abroad to improve the transfer of effective HIV interventions among communities, particularly research on the adoption and adaptation of efficacious HIV interventions by communities (including studies of diffusion processes and the exchange of knowledge between service providers and researchers); this research includes study of the maintenance of effective interventions and assessment of the generalizability of interventions with diverse populations.
- Evaluate novel interventions identified as high priority by HIV community planning groups and other service providers.
- Support research on the long-term impact of HIV prevention interventions on individuals and communities (i.e., 5 or more years postintervention).

### **Systems**

- Support research to understand and improve the organization, financing, management, access, delivery, cost-effectiveness, and cost-utility of health care (including care for substance abuse and other psychiatric disorders), family planning, and other social services that reduce HIV risk behaviors and HIV transmission.
- Support research to understand and improve prevention services' linkages, coordination, and integration with primary medical and dental care; drug, alcohol, and mental health treatment; sexually transmitted infection (STI) treatment; reproductive health and family planning services; services for orphans and vulnerable children, and other social services.
- Support research on integrating HIV prevention interventions into drug addiction treatment settings, with emphasis on behavioral treatments, alone or in combination with pharmacotherapies, for both HIV-positive and HIV-negative drug users.

- Support intervention research on strategies for improving the willingness of communities to adopt and sustain primary prevention interventions.

**Methods**

- Design and test behavioral interventions for relevant populations to increase recruitment, retention, and adherence to protocols for HIV prevention research, including trials studying prophylactic vaccines, microbicides, and other biomedical prevention methods.
- Encourage, where appropriate, the use of quasi-experimental designs and the evaluation of natural experiments in domestic and international HIV intervention research.
- Support behavioral intervention studies that include HIV seroincidence data and other biologic markers as outcome measures.

## **OBJECTIVE-B**

**Conduct basic social and behavioral research on factors influencing HIV risk behaviors and on the consequences of HIV disease: Support basic social and behavioral research to strengthen understanding of the determinants, processes, and cultural and contextual issues influencing HIV-related risk and protective behaviors and the consequences and impact of HIV disease, including treatment for and management of HIV infection. This includes domestic and international research that examines the societal, community, organizational, social network, dyadic, and individual barriers to and facilitators of the adoption and utilization of effective preventive and treatment interventions across the life course.**

## **STRATEGIES**

### **Continuing Critical Areas**

- Conduct basic research to understand better the impact of HIV therapeutic regimens on adherence to treatment for HIV and cooccurring infections, sexual risk behaviors, drug-related risk behaviors, and psychosocial adaptation (i.e., improved quality of life).
- Examine brain mechanisms that underlie HIV risk behaviors, such as how the brain processes and uses representations of long-term consequences of behavioral choices to guide immediate behaviors.
- Develop new models of behavioral change that integrate biological, psychological, and social perspectives to explain and predict the adoption and maintenance of HIV risk and HIV protective behaviors among vulnerable individuals and understudied groups, both domestically and internationally.
- Support theory-building studies developed in the context of HIV prevention research.
- Support research that can more closely monitor the HIV/AIDS epidemic and associated risk behaviors so that emerging needs for basic behavioral and intervention research can be identified.

### **Consequences**

- Support research on the decisionmaking processes and behaviors of health care workers regarding the offering of HIV counseling, testing, and other prevention services, as well as the prescription of HIV disease treatments, to those in need of HIV services and care; investigate the relationships between the health care workers' decisions and those of patients, family members, and community members.
- Conduct research concerning the health and life course of children, including orphans, affected by HIV. This research should include early identification and assessment of affected children for physical, psychological, and social consequences.
- Identify the neurobiological, behavioral, cognitive, social, and economic consequences of HIV disease for HIV-seropositive individuals (including children), their support systems (e.g., partners, family members, and other caregivers), health care systems, and communities.
- Support research on the economic and social implications for retired and older individuals who provide support and care to younger family members or friends with HIV/AIDS and their dependents.
- Support behavioral research to study end-of-life transition strategies for patients with HIV/AIDS and their caregivers.

- Support interdisciplinary research, involving behavioral and biomedical scientists, to determine the relationships among stress, mood disorders, immune system functioning, and HIV infection, and to examine the psychosocial and physiological factors affecting those relationships.
- Support studies on animal models of behavior and behavioral change relevant to HIV infection and prevention; in particular, conduct behavioral neuroscience and neuropsychological research to determine the brain/behavior changes associated with exposure to HIV, the effects of HIV exposure on social behaviors (e.g., mother-infant attachment and peer interactions), and behavioral changes in relation to comorbidities of HIV and substance use and addiction.

## Prevention

- Study the acquisition and maintenance of HIV-related risk and protective behaviors associated with HIV transmission or progression in specific social and cultural contexts, such as the sexual dyad, peer groups, social and substance-using networks, families, and communities. This would include studies of HIV risk, transmission, and progression as related to cultural norms that affect disempowerment of and violence toward women.
- Study how HIV risk might change over time as a function of developmental and life-course events, such as adolescence, childbearing, marriage or entry into other committed partnership, divorce and separation, and aging.
- Conduct research on decisionmaking processes that relate to sexual and drug-related risk-taking across the life course (e.g., individual and dyadic decision processes concerning whether and under what circumstances to have sexual intercourse; risk assessment of self and partner; the weighing of pregnancy prevention, HIV prevention, and relationship goals in choosing to use a condom and/or other method) and decisionmaking processes related to sharing needles or other drug paraphernalia and having sex with someone who may be infected.
- Support multidisciplinary research that investigates the biobehavioral and sociobehavioral determinants of sexuality, including processes of sexual and gender identity formation, as they relate to HIV risk.
- Conduct research on partner selection and relationship dynamics, including how partner choice, partner formation, relationship development, and partner stability change over the life course and affect HIV risk and HIV-related behavior; studies should examine psychological, cultural, and social factors that influence these phenomena. Interactions of alcohol/drug use with partner selection and demographic trends in partnering, as related to HIV risk, should also be addressed.
- Support multidisciplinary research that investigates biobehavioral and sociobehavioral determinants of injection drug use and the transition from noninjection to injection drug use as they relate to HIV transmission; such research may also include studies that investigate the relationship between any drug use and sexual risk behaviors.
- Conduct research on individual social and cultural differences in human sexuality that have an impact on the sexual transmission of HIV; such research may include studies that examine how sexual behavior is affected by substance use and abuse, sexual abuse or coercion, developmental processes, and the formation and dissolution of intimate relationships.
- Study the social, structural, cultural, and demographic factors (e.g., socioeconomic status, marital status, ethnicity, sexual identification, age, and gender) that influence HIV-related behavior.
- Support research to understand how and whether communities engage in HIV preventive interventions, including studies to determine how to better ensure the use of prevention research by communities and public health entities in the United States and abroad.

- Support research that investigates the impact of laws and policies on behaviors associated with HIV transmission and acquisition.
- Conduct research that identifies the social and behavioral factors affecting recruitment, retention, and adherence to prevention and treatment interventions, including clinical trials of HIV-related vaccines, microbicides, and therapeutics.
- Support behavioral and social research on the acceptability, initiation, and use of biomedical and barrier HIV prevention methods (e.g., condoms, microbicides, rapid tests, and vaccines), and determine their impact on adherence to risk-reduction guidelines.
- Support basic and preintervention research on behavior modification and maintenance of new behavioral patterns for developing prevention and intervention strategies.
- Support behavioral surveillance research that measures changes in norms and attitudes regarding behaviors associated with HIV transmission and acquisition.
- Support research to identify how alcohol use (e.g., binge drinking trends) affects HIV risk among selected age groups.
- Study factors that enhance or preclude partner notification and the impact of partner notification on HIV testing and risk reduction.

## OBJECTIVE–C

Conduct treatment, health, and social services research for people infected and affected by HIV: Support research into the development, evaluation, diffusion, and adoption of strategies to increase early identification of HIV infection; to improve treatment adherence; and to prevent or minimize the negative physical, psychological, cognitive, and social consequences of HIV infection, including stigmatization of persons with or at risk for HIV infection. Support research strategies for promoting effective health care utilization among all persons with HIV infection and for promoting modifications in the health care delivery system to develop more effective, socially appropriate, and culturally sensitive methods to better serve treatment needs of infected populations, both domestically and internationally.

## STRATEGIES

### Treatment and Care

- Develop and test interventions to modify the practice behaviors and decisionmaking processes of health care providers to improve the quality of screening, counseling, and treatment services for HIV-positive persons and persons at risk for HIV infection.
- Support research on adherence to treatment regimens, including studies on communication techniques to improve shared decisionmaking between health care providers and HIV infected individuals, issues such as how and when to initiate, interrupt, or cease therapy, and behavioral strategies to manage symptoms secondary to treatment protocols.
- Promote research to identify and remove barriers to effective health care utilization among persons with or at risk of HIV infection, including barriers associated with access, engagement, followup, and adherence to health and social services across the care continuum (e.g., early identification of HIV infection, testing and counseling, health-care-seeking behavior, adherence, case management, and home/hospice care) and across the life course (i.e., from childhood to old age).
- Develop and test interventions to increase recruitment, adherence, and retention in HIV/AIDS clinical trials and care by HIV infected persons from all vulnerable populations, with special attention to developmental and life-course issues.
- Support health services research and evaluation research to determine the impact of changes in the health care delivery system on HIV/AIDS care.
- Support research to foster more effective participation in treatment planning, decisionmaking, and formulating advance directives by patients with HIV and their families.

### Biopsychosocial Consequences

- Develop and evaluate interventions to prevent the adverse psychological and social consequences of HIV infection and to assist HIV affected populations in coping with HIV infections, maintaining quality of life, and avoiding engagement in HIV-related risk behaviors.
- Test interventions to address the neuropsychological, neurodevelopmental, and psychiatric sequelae of HIV infection.
- Develop and evaluate interventions to minimize the impact of stigmatization on HIV infected persons, including on their decisions regarding treatment and quality of life.

- Test interventions designed to support formal and informal caregivers and family members of HIV infected persons in order to prevent, for example, depression and burnout.
- Support research to enhance the quality of life and minimize the impact of pain, fatigue, physical symptoms, and treatment side effects and to integrate effective palliative care throughout the course of treatment for all people living with HIV and AIDS.

## OBJECTIVE-D

**Improve the quality of behavioral and social science methodology in HIV research: Support research to advance innovative quantitative and qualitative methodologies to enhance behavioral and social science on HIV prevention and care, and to address pressing ethical issues in the conduct of such research.**

## STRATEGIES

### Measurement

- Develop improved methodologies—including methods for obtaining and validating self-report data, culturally appropriate standardization of measurement tools for surveys, and the measurement of change over time—based on an assessment of the current status of qualitative and quantitative methodologies for studying behavioral and social factors associated with HIV and AIDS.
- Develop and strengthen research instruments that are culturally and linguistically appropriate for subpopulations (e.g., HIV infected children, the elderly, and prisoners) and that reflect age-appropriate concerns.
- Develop and refine techniques for measuring social networks associated with HIV transmission.
- Support research to determine under what circumstances each of the following outcome measures—alone or in combination—is appropriate to use: self-report measures, HIV infection, and other disease outcomes such as other STIs and blood-borne diseases.
- Develop improved qualitative approaches to theory building and to measurement of HIV-related behaviors, behavioral change, and factors that influence behavior and behavioral change.
- Develop improved approaches to formulate, integrate, and analyze theories founded on qualitative and quantitative observations.
- Develop and refine outcome measures and indicators appropriate for the evaluation of social policy and the societal impact of HIV prevention and treatment interventions.

### Modeling

- Develop and refine mathematical models for linking behavioral change interventions with a reduction in HIV transmission at different levels of seroprevalence.
- Improve methods for forecasting and modeling AIDS caseloads, health care needs, and health care utilization under different treatment and survival scenarios and for forecasting and modeling prevention services needs.

### Design and Statistical Analysis

- Develop improved sampling strategies for subpopulations (e.g., children, homeless persons, drug users, the elderly, and gay men of color).
- Develop improved and innovative methods and techniques for conducting and analyzing longitudinal studies of HIV-vulnerable and HIV infected populations, including improved participant retention strategies; statistical methods for dealing with participant attrition, missing data, and nonnormal distributions; and methods for measuring and analyzing nonlinear patterns of behavior change.

- Foster the development and dissemination of design alternatives to the randomized controlled trial that permit cost-effective evaluation of intervention strategies at the individual, group, and community levels.
- Foster the development, maintenance, and use of shared databases that will enhance the ability to identify and detect significant interactions between and within a variety of behavioral domains and also to identify the role of behavioral actions as mediators of biological outcomes of importance in HIV research.

#### **Ethics and Other Issues**

- Evaluate the effects of legal and ethical constraints on methods of HIV research and service delivery, particularly among vulnerable or special populations.
- Develop and refine research techniques to advance multisite, intercultural, and international studies.
- Encourage secondary data analysis; develop approaches to protect and document confidentiality.
- Develop and evaluate mechanisms for dissemination of behavioral research findings to the HIV/AIDS research and service communities and for receiving and evaluating community or constituent feedback.

## CHAPTER 3

# Therapeutics



**AREA OF EMPHASIS**

# Therapeutics

**SCIENTIFIC OBJECTIVES AND STRATEGIES****OBJECTIVE–A**

Identify and validate viral and cellular functions required for HIV replication that can be targeted for viral inhibition, clearance, and prevention of transmission. Discover and develop novel agents and therapeutic strategies directed against viral and host factors involved in HIV transmission, infection, replication, and persistence. Encourage collaborations between academia, industry, and the NIH.

(The scientific objectives of A and B are of equal weight.)

**STRATEGIES**

- Identify, characterize, and validate new and understudied viral and host targets for anti-HIV therapy (e.g., factors involved in viral fusion, entry, integration, transcription, replication, assembly, budding, infectivity, virulence, and pathogenicity). Develop predictive test models, including appropriate lentivirus animal models, to aid in identifying agents and strategies active against these targets.
  - ▶ Develop agents (including natural products) and treatment strategies that target, inhibit, and clear HIV in cellular, anatomical, and organ reservoirs and sanctuaries.
  - ▶ Characterize potential agents, including their preclinical, immunologic, pharmacokinetic, pharmacodynamic, toxicity, and teratogenicity profiles.
  - ▶ Develop new compounds and chemical formulations, including microbicides and other methods, suitable for the genitourinary and gastrointestinal tracts.
  - ▶ Employ whole animal and ex vivo organ or tissue models of lentivirus infections to study the biologic and pharmacologic characteristics of therapeutic agents.
- Acquire structural information on HIV and cell constituents involved in HIV infection for the design of potent therapeutic agents and therapeutic vaccine candidates with activity against drug-resistant strains. Post lead structures on publicly accessible databases in real time.
  - ▶ Integrate genomics and informatics paradigms, concepts, and methodologies (microchip-based screens and analyzers) into mainstream drug discovery and development of therapeutic entities and strategies.
  - ▶ Develop enabling technologies to accelerate and optimize the discovery and development of therapeutic entities and strategies; establish the infrastructure to provide services and reagents needed by the scientific community.
  - ▶ Evaluate the intracellular pharmacokinetics and activity of antiretroviral (ARV) agents in different cell types, different stages of the cell cycle, and in all age groups. Correlate intracellular pharmacokinetic parameters with drug efficacy/toxicity.

- ▶ Develop agents with desirable biopharmaceutical characteristics (e.g., improved bioavailability and tissue penetration to the central nervous system [CNS] and other sanctuaries); develop drug delivery devices or systems that improve the pharmacokinetic profile of therapeutic agents, target specific organs or tissues, reduce toxicities and adverse effects, and result in improved adherence to therapeutic regimens.
- Study the mechanisms and implications of drug resistance and viral fitness; evaluate early markers and genotypic mutations that lead to resistance and cross-resistance.
  - ▶ Advance basic and applied gene-based strategies to treat HIV infection. Foster new approaches and technologies to optimize gene delivery that results in regulated and persistent gene expression. Optimize *ex vivo* gene delivery and advance new concepts, strategies, and vectors for direct *in vivo* delivery.
  - ▶ Develop mathematical and computer models of HIV infection and therapeutic interventions that stimulate and predict *in vivo* efficacy, toxicity, and other outcomes of drug regimens and clinical trials. Investigate the use of pharmacogenetics in identifying optimum therapies.
  - ▶ Investigate the host cell effects of ARV drugs.
- Develop and perform the preclinical evaluation of fixed dose combination formulations of approved ARV drugs, including doses appropriate for children.
- Develop and evaluate pediatric drug formulations of available and new ARV drugs, with emphasis on low dose dividable solid formulations appropriate for use in resource-limited settings, as well as liquid formulations.

## OBJECTIVE–B

Conduct clinical trials (including the development of new methodologies) in domestic and international settings, especially in resource-developing nations, to: (1) evaluate the short- and long-term efficacy and effectiveness of therapeutic agents and strategies against HIV infection and transmission in treatment-naïve and treatment-experienced HIV infected individuals; and (2) develop strategies to mitigate factors that adversely affect the success of therapeutic strategies against HIV infection. Develop domestic and international partnerships to design and conduct clinical studies where the epidemic is prevalent.

(The scientific objectives of A and B are of equal weight.)

## STRATEGIES

### Clinical Trials of Therapeutic Agents

- Conduct clinical trials of potential therapeutic agents and combinations of agents in adults, adolescents, and children to determine pharmacokinetics, tissue bioavailability, antiviral activity, effects on the immune system, safety, and clinical efficacy.
  - ▶ Evaluate optimal combinations of agents selected for antiviral synergy, complementary mechanism of action, minimal toxicity and cross-resistance, simplicity of administration, and tolerability.
  - ▶ Evaluate optimal therapies and strategies for individuals who have acute or recent infection (including neonates/young infants with perinatal infection), chronic infection but no prior antiretroviral therapy (ART), and those with prior ART including individuals with multiple drug-resistant virus.
  - ▶ Support clinical trials to study:
    - long-term effectiveness (including toxicities) of therapeutic strategies;
    - timing, selection, and strategic sequencing of ARV agents to optimize clinical outcome; and
    - optimal treatment for heavily ARV-experienced individuals with treatment failure.
  - ▶ Evaluate novel therapeutic modalities (e.g., cell-based, gene-based, and therapeutic vaccine approaches) with state-of-the-art antiretroviral therapies.
  - ▶ Evaluate coformulated ARVs.
  - ▶ Evaluate the benefits or risks of commonly used complementary agents (herbal, homeopathic, and/or naturopathic) when used concomitantly with ART.

### Clinical Trials Enrollment

- Strengthen efforts and implement new approaches to ensure the enrollment and retention of specific populations, including women, children, adolescents, minorities, substance abusers, and older adults in clinical trials to reflect the incidence of the epidemic.
- Strengthen efforts to evaluate new and existing drug treatment regimens in clinical trials that reflect the demographics of the epidemic, including traditionally underrepresented populations. When appropriate, evaluate potential gender, race, ethnicity, age-specific, pregnancy-related, and nutrition-related differences in drug efficacy and safety, including pharmacokinetics, metabolism, tissue absorption, and drug elimination.

- ▶ Identify and evaluate the viral and host factors, including human genomics, associated with ART failure including malabsorption, drug interactions, drug resistance, drug toxicities, pharmacogenetics, and suboptimal adherence.

### **Clinical Trial Methodology**

- Develop and evaluate standardized virologic, immunologic, and clinical markers to assess drug activity; determine and validate surrogate markers in response to various therapeutic interventions, including those most applicable to resource-limited settings.
- Identify and test strategies to improve the recruitment and retention of individuals in clinical trials.
- Develop, incorporate, and validate appropriate quality-of-life parameters in clinical trials of ARV agents.
- Develop methodology to facilitate cross-protocol analysis and meta-analyses.
- Conduct research on how and why subjects decide to participate in clinical trials in order to increase enrollment and maintain adherence to study protocols.
- Develop methodology for research on the ethical conduct of clinical trials.

### **Pharmacology**

- Determine the relationship between drug exposure (pharmacokinetics) and outcomes (antiviral effect, immune function, and safety) to facilitate dosing strategies within clinical trials, as well as for individual patient management.
- Investigate drug interactions among commonly used treatments for HIV-related disease and its complications, as well as other substances that may be used by HIV infected individuals.
- Investigate the effect of drug-sparing regimens on efficacy, resistance, and transmission.

### **Viral Reservoirs**

- Evaluate the presence and persistence of HIV in different tissue compartments during ART; investigate the role of anatomic and cellular sanctuaries in the development of HIV drug resistance, transmission, and establishment of long-term reservoirs.
- Evaluate the penetration of ARVs into different tissue compartments (e.g., genital secretions/semen, CNS, breast milk, etc.).

### **Viral Resistance and Fitness**

- Explore the utility of real-time ARV phenotypic and genotypic assays in managing ART across a broad spectrum of individuals.
- Evaluate the impact of transmission of drug-resistant strains of HIV on disease progression or therapy.

### **Adherence**

- Support research on the effectiveness of pharmacological approaches, behavioral interventions, and other approaches to facilitate better adherence to ARV regimens.

- Develop better methods to assess adherence to treatment regimens across a variety of affected populations; compare and validate adherence measures in the context of HIV treatment.
- Investigate strategies for managing symptoms that are attributed to therapy, and investigate the relationship between symptom management and improved adherence to ARV regimens.

### International

- Enhance the development of international collaborations that will assist in addressing relevant therapeutic research in populations of HIV infected adults, adolescents, and children.
- Assist developing nations, as appropriate, in technology transfer through training, infrastructure, and capacity building to facilitate the evaluation of ARV agents and other therapies in local settings.
- Assess the barriers to delivery of effective HIV/AIDS health care including treatment and the capability of conducting international therapeutic clinical trials through the establishment or expansion of multidisciplinary clinical centers.
- Develop and evaluate simpler, reliable, user-friendly, and inexpensive surrogate markers and assay technologies for monitoring immunologic and virologic status and ARV drug responses that can be used in resource-limited settings.
- Develop standardized clinical indicators to determine how and when to initiate ART, to monitor responses to therapy, and to determine when to change therapy.
- Determine acceptable laboratory monitoring for drug toxicity in resource-limited settings.
- Evaluate whether nutritional status (particularly chronic malnutrition) affects the efficacy of therapy and whether it affects the risk or severity of adverse events associated with ART.

## **OBJECTIVE–C**

**Develop strategies to evaluate, prevent, predict, and treat complications and toxicities of antiretroviral treatment in domestic and international settings.**

## **STRATEGIES**

- Evaluate potential delayed or late effects of ART following short-term administration of prophylaxis regimens, as well as during chronic treatment.
- Support research on the pathogenesis and mechanisms of toxicity of drugs used to treat HIV disease.
- Develop and test approaches to prevent or reverse potential metabolic abnormalities (e.g., changes in body composition, development of atherogenicity and endocrine disorders, and changes in bone and muscle structure) based on an understanding of the mechanisms by which ART and/or suppression of HIV replication may affect metabolic processes.
- Integrate metabolic, endocrine, cardiovascular, neurologic, renal, and bone studies into ongoing and planned treatment trials which may provide an opportunity to answer important questions related to potential complications of ART.
- Develop approaches to monitor and evaluate the effects of gender, race, age, pregnancy status, and type of exposure on complications of ART.
- Evaluate the impact of nutritional deficiencies, impaired access to safe drinking water, regionally significant coinfections, and other population- and area-specific factors on complications of ART in developing countries.
- Evaluate the impact of nutrition and nutritional interventions in undernourished populations or lactating mothers provided concurrently with ART on improved clinical outcomes.
- Evaluate drug interactions with potential clinical significance for HIV infected individuals, particularly the pharmacokinetics and pharmacodynamics between ARVs, drugs to prevent and treat coinfections (particularly tuberculosis), and medications used in the treatment of drug addiction and mental disorders; develop strategies to avoid or minimize the clinical impact of these interactions.

## OBJECTIVE–D

Develop and evaluate new agents and strategies for preventing and treating hepatitis B virus (HBV), hepatitis C virus (HCV), tuberculosis (TB), Epstein-Barr virus (EBV), human papillomavirus (HPV), malaria, and the most significant coinfections in the context of HIV disease in domestic and international settings.

(The scientific objectives of D and E are of equal weight.)

## STRATEGIES

### Preclinical Discovery and Development

- Support preclinical drug design and development programs to develop therapies against associated pathogens, especially HBV, HCV, Kaposi's sarcoma herpesvirus/human herpesvirus (KSHV/HHV-8), HPV, EBV, cytomegalovirus (CMV), malaria, and *Mycobacterium tuberculosis*, with emphasis on innovative approaches and agents with favorable bioavailability and pharmacokinetics, as well as development of formulations appropriate for use in children.
- Support and encourage mechanism-based screening of novel synthetic compounds and natural products to identify candidate agents for treating the most significant coinfections requiring Federal Government support; provide support for medicinal chemistry, structural databases, resynthesis, and toxicity testing.
- Cooperate with the private sector to increase involvement and investment in anti-opportunistic infection (OI) and anti-coinfection drug discovery and development research, especially in areas where public health needs are substantial; assume full responsibility, when necessary, for the development of potential therapies with high public health relevance and need.
- Continue to support studies and develop vaccines and interventions for coinfections (e.g., TB, HPV, Rotavirus) in HIV infected children, adolescents, and adults.

### Clinical Trials of Therapeutic Regimens

- Assess the impact of new ARV regimens on the risks for and manifestations of infections associated with HIV/AIDS in adults, adolescents, and children.
- Improve our understanding of the interplay between HIV-associated immune deficiencies and the onset and types of infectious complications.

### Clinical Trial Methodology

- Improve strategies for prevention of multiple infections in the context of ART; determine the optimal timing for initiating/discontinuing prophylaxis for different OIs and coinfections; develop improved strategies to minimize toxicities and the development of drug-resistant microorganisms.
- Develop tools to identify HIV infected individuals at high risk for development of specific OIs and coinfections, to improve the efficiency of clinical trial design and the risk/benefit ratio of the currently utilized drugs for prophylaxis and for treatment.
- Develop clinically useful assays and methodologies for early and rapid diagnosis of OIs and coinfections, quantitative assessment of microbiological responses, and drug sensitivity testing.

### **Coinfections**

- Support research on the interactions between ART and coinfections.
- Study the interaction between HIV infection and infectious complications upon pathogenesis, presentation, and disease outcomes in adults, adolescents, and children.
- Support clinical trials, domestic and international, of adults and children coinfecting with HIV and TB (both active and latent infection). Evaluate safety and efficacy of treatment regimens in coinfecting individuals. Determine optimal length of treatment. Evaluate regimens in the context of degree of immunosuppression.
- Investigate surrogate markers of TB disease that could distinguish between latent, active, and eradicated infection in coinfecting individuals; determine how each infection influences or alters the other disease in respect to progression and response to therapy.
- Support clinical trials investigating the efficacy and risks of treatment of HCV in individuals who are coinfecting with HIV; determine how each infection influences or alters the other disease in respect to progression and response to therapy.
- Study the interaction of coinfections with HIV transmission (e.g., placental malaria and perinatal infection) and effects on HIV disease progression.

### **Pharmacology and Toxicology**

- Conduct preclinical studies of anti-OI and anti-coinfection drugs (alone or in partnership with industry) to assess their immunologic, pharmacokinetic, pharmacodynamic, toxic, reproductive, and teratogenic effects, as well as transplacental carcinogenicity; develop pediatric formulations of anti-OI drugs, including lower dose solid as well as liquid preparations.
- Support clinical studies to evaluate the safety and pharmacokinetics of existing and experimental agents intended to treat or prevent OIs and coinfections in HIV infected infants, children, and pregnant women.
- Evaluate drug interactions between anti-TB agents and HIV medications. Support the investigation of new anti-TB agents with fewer side effects, drug interactions, and/or action against multiple drug-resistant TB.

### **Adherence**

- Support research on the effectiveness of pharmacologic and other approaches in promoting adherence to anti-coinfection regimens.
- Develop formulations, routes of administration, and delivery systems for existing and experimental anti-OI and anti-coinfection drugs appropriate for use in infants, children, and other populations.
- Develop and evaluate interventions to facilitate better adherence to therapies among populations with HIV infection and substance abuse and/or mental illness.
- Investigate strategies for managing symptoms that are attributed to HIV infection, coinfection, and/or therapy, and investigate the relationship between symptom management and improved adherence to ARV regimens.

**International**

- Conduct clinical trials in adults and children to evaluate agents for the prophylaxis and treatment of HIV-associated OIs and coinfections; target infections shown to cause significant morbidity by epidemiologic studies, and made worse by HIV-induced immunosuppression.
- Develop and evaluate strategies for treatment and prevention of prevalent opportunistic and endemic infections in the context of HIV infection.
- Evaluate the role of nutrition, malnutrition, and severe malnutrition on treatment and prophylaxis regimens for OIs and coinfections.

## OBJECTIVE-E

Develop, evaluate, and implement strategies for interrupting mother-to-child transmission (MTCT), applicable to resource-limited and -rich countries, with emphasis on strategies to interrupt transmission through breastfeeding, the short- and long-term effects of interventions for interrupting MTCT on the health of women and infants, and development of drug resistance after antiretroviral MTCT prophylaxis and its effect on subsequent antiviral therapy and efficacy in future pregnancies.

(The scientific objectives of D and E are of equal weight.)

## STRATEGIES

### Mechanisms of Transmission

- Investigate the mechanisms and timing of MTCT to facilitate and develop targeted drugs/strategies to further decrease MTCT or provide alternatives to currently identified effective strategies.
- Investigate risk factors (e.g., immune, viral, and host-related) associated with breast milk HIV transmission.
- Develop reproducible, sensitive, and specific assays to detect and quantitate the amount of cell-free and cell-associated virus in breast milk.

### Interventions and Trials to Evaluate Interventions to Reduce Transmission

- Use and/or develop suitable animal models to evaluate novel strategies to prevent transplacental and postpartum breastfeeding transmission of HIV, and to evaluate transplacental passage of ARV agents and their effects on placental function and on fetal development and viability.
- Develop safe and conveniently administered strategies to interrupt MTCT using interventions that are affordable in resource-limited nations, including specific strategies to prevent postnatal transmission of HIV through breast milk by providing prophylaxis to the infant, mother, or both during the lactational period.
- Evaluate the pharmacokinetics and safety of ARV drugs in pregnant women and their fetuses/infants, and the penetration of ARV drugs into breast milk and genital fluids.
- Evaluate strategies for reducing MTCT when maternal antepartum and intrapartum ART is not given or available (e.g., postpartum prophylaxis of the infant only).
- Support international collaborative efforts to conduct clinical trials of interventions to interrupt MTCT.
- Develop and evaluate strategies for reducing the risk of vertical transmission of HIV from pregnant women to their offspring, and evaluate the impact of that intervention on maternal health treatment options; such strategies may include antiviral agents, anti-HIV immunoglobulin, monoclonal antibodies, agents targeted to cellular targets (e.g., blocking cytokine receptors), cell- and gene-based strategies, vitamin supplementation, HIV vaccines, adjuvants, and virucides, alone or in combination.
- Study the effects of ARV regimens used for maternal health indications on the risk of vertical transmission (including postnatal transmission through breast milk).
- Support research and development of new clinical trial designs, statistical methodologies and investigation of biologic markers, surrogates, and/or other outcomes to evaluate the activity, clinical efficacy, or reasons for failure of new agents and approaches in the treatment of HIV infected pregnant women and their offspring.

### Issues Related to Antiretroviral Drug Resistance

- Evaluate the effects of preexisting viral drug resistance in pregnant women on the effectiveness of ARV regimens to prevent MTCT.
- Evaluate the risk for the development of HIV variants with detectable antiretroviral drug resistance in pregnant women who receive different types of ARV prophylactic regimens and the kinetics and durability of such resistance in cell-free and cell-associated virus in plasma, breast milk, and genital secretions.
- Evaluate the risk for development of HIV variants with detectable antiretroviral drug resistance in infants who become infected despite maternal receipt of ARV prophylaxis regimens and the kinetics and durability of such resistance in cell-free and cell-associated virus.
- Evaluate the effects of developing drug resistance following ARV prophylaxis on the health and response to future ART in women and infants who become infected with HIV despite prophylaxis.
- Evaluate the effect of drug resistance developing following ARV prophylaxis in an initial pregnancy on the efficacy of the prophylactic regimen in reducing transmission in subsequent pregnancies.
- Evaluate effective, safe, simple, and short alternative antiretroviral regimens that have lower risk of development of resistance in women or infants infected despite prophylaxis than those currently used for prevention of MTCT in resource-limited settings.
- Evaluate the public health impact of ARV resistance that develops in pregnant HIV infected women secondary to use of ARVs solely for prevention of MTCT.

### Issues Related to Short- and Long-Term Effects of ARV Prophylaxis for Reducing MTCT

- Evaluate the short-term toxicities, pharmacokinetics (including transplacental drug transfer to fetus/infant), and ARV activity of new agents, existing agents, and combinations of agents in pregnant HIV infected women and their neonates.
- Evaluate whether pregnancy increases the risk of potential ARV toxicities, the pathogenesis of such toxicities in pregnancy, and clinical findings or laboratory assays that might be predictive of such effects.
- Study the effects of ARV regimens used during pregnancy for treatment of maternal HIV disease on maternal health and pregnancy outcome.
- Evaluate the optimal regimen(s) for preventing MTCT in women who are receiving ART for the sole purpose of preventing perinatal transmission, and short- and long-term clinical, immunologic, and virologic effects of receiving ART during pregnancy in such women who choose to discontinue ART after delivery.
- Evaluate the short- and long-term clinical, immunologic, and virologic effects in women who receive ART during lactation solely to prevent breast milk transmission, but who discontinue treatment following weaning.
- Evaluate the potential mechanisms for possible carcinogenic or mutagenic effects of *in utero* ARV exposure.
- Evaluate the pathogenesis of potential ARV toxicities (e.g., mitochondrial toxicity, bone toxicity) in uninfected, HIV-exposed infants with perinatal ARV exposure, and develop animal models or laboratory assays that might be predictive of such effects with exposure to an individual ARV agent alone or in combination with other ARVs.
- Develop better clinical algorithms and laboratory assays to diagnose/assess mitochondrial toxicity associated with ARV exposure in human infants and children.

- Develop and implement feasible studies that assess the long-term effects of *in utero* and/or postpartum exposure to ARVs on both HIV infected and uninfected children, both domestically and internationally.

#### **Implementation Issues**

- Develop and evaluate strategies for implementation of effective perinatal transmission prevention interventions in developed and developing countries, including ways to increase availability and acceptability of prenatal HIV testing and of prophylaxis to prevent MTCT.
- Improve the sensitivity and specificity of diagnostic procedures that are accessible, cost-effective, and have utility in developed and developing settings to permit the earliest possible determination of HIV infection in infants, and whether ARV and/or immunopreventive therapies affect the timing and sensitivity of these assays for diagnosis.
- Evaluate innovative methods, including rapid HIV antibody testing, to identify HIV infection in pregnant women with unknown HIV serostatus who present in labor, and to assess the acceptability of such testing and acceptability and efficacy of ARV prophylaxis to reduce MTCT, when administered to the woman intrapartum and her infant, or to her infant alone.
- Evaluate the public health impact of programs to prevent MTCT.

**OBJECTIVE-F**

Evaluate the impact of antiretroviral and immunotherapeutic strategies and their roles in the prevention of horizontal HIV transmission (e.g., sexual, noninjection drug use, or injection drug use [IDU] transmission) in appropriate domestic and international settings.

(The scientific objectives of F and G are of equal weight.)

**STRATEGIES****Mechanisms of Transmission**

- Evaluate the influence of drug resistance on the efficacy of ARV regimens to prevent sexual transmission.
- Use and/or develop suitable animal models and clinical studies to evaluate genital and anal passage of ARVs.
- Evaluate the influence of systemic HIV treatment on viral shedding in the anogenital tract.
- Evaluate the impact of anti-STI (sexually transmitted infection) treatment on transmission of HIV and HIV shedding in the anogenital tract.

**Interventions to Reduce Transmission**

- Support domestic and international collaborative efforts to conduct trials of ARV, immunotherapeutic, and other treatment interventions with an endpoint of horizontal transmission in acute and chronic infection.
- Develop and evaluate strategies for reducing the risk of sexual transmission of HIV without compromising treatment of the HIV infected individual; such strategies may include antiviral agents, therapeutic vaccines, anti-HIV immunoglobulin, monoclonal antibodies, immunotherapeutic agents, and microbicides, alone or in combination.

**Issues Related to ARV Interventions**

- Evaluate the risk for developing antiretroviral drug resistance (in cell-free and cell-associated virus, and in sequestered genital or anorectal sites) when using ARVs in interventions to reduce horizontal transmission, including the development of antiretroviral drug resistance in individuals who become HIV infected while receiving such therapy or in HIV infected individuals being administered such therapy solely to reduce horizontal transmission.
- Evaluate the public health impact of regimens to reduce horizontal transmission.

## **OBJECTIVE–G**

**Develop and evaluate therapeutic approaches, including therapeutic vaccine candidates, that will restore and sustain a competent immune system in HIV infected individuals in domestic and international settings.**

**(The scientific objectives of F and G are of equal weight.)**

## **STRATEGIES**

- Employ approaches to enhance immune restoration in clinical trials; test specific hypotheses of HIV immunopathogenesis.
- Evaluate the capacity of the immune system to maintain or repair itself after maximal effective viral suppression.
- Evaluate immune-based therapies for the purpose of improving ART-sparing regimens, permitting delay in initiating or reinitiating ART.
- Develop, validate, and standardize new methods for evaluating immune function in clinical trials that enroll adults, adolescents, and children, including assays that may be used in resource-limited settings.
- Accelerate the preclinical and clinical testing of cytokines, modulators of cytokines, combinations of broad-based neutralizing monoclonal antibodies, and immunoactive agents to prevent further immune deterioration, to reconstitute deficient immune systems, and to enhance the immunogenicity of therapeutic HIV vaccines.
- Develop and evaluate active and passive immunotherapeutic approaches for HIV infection and its sequelae, including the testing of optimum immunogens; determine best patient disease status for response, most effective immunization dose and schedule, and most meaningful readout of clinical impact of the intervention.
- Support research on approaches to facilitate better adherence to immunoactive regimens.
- Evaluate the safety and efficacy of administering cellular immune elements, including use of expanded and/or modified peripheral blood T cells, bone marrow, cord blood stem cell transplantation, and thymic transplantation.
- Evaluate the immune system after partial restoration by effective ART. Define qualitative and quantitative differences between the restored immune system and the naive immune system to determine if identified deficiencies can be diminished by immunoactive agents including the use of vaccines for specific OIs and coinfections.
- Develop new therapeutic strategies based on gene delivery strategies to protect mature, hematopoietic stem cells, hematopoietic pluripotent cells, and stromal cell elements from destruction by HIV.
- Evaluate the potential to inhibit HIV replication and spread by modifying chemokine receptor expression and/or chemokine levels. Develop agents to block the attachment of HIV to receptors and coreceptors and thus inhibit entry into cells.
- Study the mechanisms of action of immunomodulating agents, and proceed with applied studies and development of the most promising approaches.
- Evaluate immunologic markers that may identify individuals at risk for late complications of therapy.
- Develop standards and definitions to allow better comparisons of late complications across clinical trials.
- Evaluate immune-based therapy as an adjunct to salvage therapy strategies.
- Identify immunological predictors of *in vivo* immune control of viral replication.

**OBJECTIVE–H**

**Develop strategies for assessing, preventing, and treating HIV nervous system infection and central and peripheral nervous system manifestations of HIV disease in domestic and international settings.**

(The scientific objectives of H, I, and J are of equal weight.)

**STRATEGIES**

- Develop therapeutic agents to block HIV entry into the CNS and treat HIV infection in the CNS; develop and evaluate novel strategies such as neuroprotective agents that are active against putative pathways of HIV-induced CNS dysfunction in adults, adolescents, and children.
- Design and conduct clinical trials addressing nervous system complications of HIV infection and treatments in adults, adolescents, and children.
- Develop and utilize *in vitro* and animal models of CNS lentivirus infections and CNS injury to identify therapeutic agents for the nervous system complications of HIV infection.
- Assess the pathogenic role of viral sequestration in the CNS, including its potential role as a reservoir of viral persistence and as a site of independent selection of antiviral drug-resistant strains and other mutants.
- Determine the incidence and prevalence of HIV-associated neurologic disease after long-term ART.
- Develop objective quantitative assessments (e.g., surrogate markers in cerebrospinal fluid [CSF] and neuroimaging) of treatment effects.
- Characterize the CNS pharmacokinetics and pharmacodynamics of ARVs; determine the importance of CNS drug penetration, particularly penetration of the blood-brain barrier, in reducing CNS infection in neurologically symptomatic and asymptomatic subjects.
- Develop strategies for manipulating drug transporters at the blood-brain barrier to facilitate entry of ARVs into the CNS compartment.
- Develop better strategies including complementary and alternative medicine approaches to prevent, diagnose, and treat peripheral neuropathies in HIV infected individuals.
- Improve existing and develop novel sensitive, reliable, and valid measures of neuropsychological performance having cross-cultural and international applicability and sensitivity to HIV neurological insult and ARV treatment.
- Determine the prevalence, causes, and pathogenesis of pain in HIV infected individuals and develop optimal therapies for pain management.
- Monitor CSF for HIV viral load and immune activation markers in individuals enrolled in studies of ART.
- Further elucidate the correlation among CSF HIV viral load, chemokine levels, proinflammatory cytokines, and markers of immune activation with CNS disease in clinical trials.
- Support the research and development of new statistical methodologies, clinical trial designs, and selection and investigation of biologic markers, to evaluate the safety and clinical efficacy of new agents and approaches in the treatment of neurologic and cognitive complications of HIV disease.

- Support research on the effectiveness of pharmacologic and other approaches to facilitate better adherence to therapeutic regimens in neurologically impaired individuals.
- Evaluate the effectiveness of reducing HIV-associated CNS disease burden by therapeutic agents currently used to treat other neurologic diseases (e.g., Parkinson's and Alzheimer's disease) that may share pathophysiologic features with HIV-associated neurologic disease.
- Develop, incorporate, and validate functional neurologic and quality-of-life scales that are aimed at measuring the impact of nervous system complications of HIV infection in clinical trials.
- Assess the incidence and prevalence of HIV-1 and HIV-2 induced neurological and neurobehavioral complications, and assess the impact of other viral, bacterial, fungal, or parasitic infections on HIV disease in the CNS.
- Conduct viral genetic analyses of HIV derived from CNS sources (including studies of the role of HIV-1 non-B subtypes and HIV-2) in causing neurologic, cognitive, and neurobehavioral dysfunction.
- Determine anatomical, structural, and genetic contributors (haplotypes, epigenetics) to neurological vulnerability to HIV infection and related inflammatory processes.
- Conduct studies to determine drug interactions between commonly used treatments for HIV disease and its complications, with treatments for drug abuse and cooccurring mental health disorders; develop treatments and regimens that are optimized for HIV infected individuals with comorbid depression and other psychiatric disorders.

**OBJECTIVE–I**

**Develop and evaluate improved strategies for the assessment, treatment, and prevention of cancer-specific manifestations of HIV disease in domestic and international settings.**

(The scientific objectives of H, I, and J are of equal weight.)

**STRATEGIES****Preclinical Drug Development**

- Promote screening, discovery, and development of novel therapeutic agents with activity against HIV-associated malignancies, including pathogenesis-based strategies, agents with better CNS penetration, and agents with better safety profiles.
- Based upon structural biologic and biochemical information, develop therapeutic agents for the treatment of HIV-associated malignancies.
- Develop preclinical and *in vivo* models for testing potential therapeutic strategies against HIV-associated malignancies.

**Diagnostic Methods**

- Develop and improve methods for early diagnosis of malignancies in the context of HIV disease and for early detection of recurrent cancer or secondary malignancies.

**Clinical Evaluation of Therapeutic and Prevention Strategies**

- Develop therapeutic and prevention strategies for HIV-associated malignancies based on an improved understanding of the role of infectious agents (e.g., KSHV/HHV-8, EBV, HPV, and HBV) in their pathogenesis.
- Continue to support studies of the efficacy of HPV vaccines to prevent and treat cervical cancer in HIV infected populations.
- Evaluate novel approaches for the treatment of HIV-associated malignancies through clinical trials, and evaluate the interactions between treatment of malignancies and treatment of the underlying HIV infection.
- Support approaches using gene- and protein-based technologies, such as tissue array and microarray, in targeting treatment of HIV-associated malignancies.
- Develop, incorporate, and validate clinical trial methodologies to correlate tumor-specific responses with clinical benefit, including quality-of-life parameters; develop a staging system indicative of prognostic response and survival.
- Identify surrogate endpoints indicative of response to therapy and novel methods for evaluating tumor response, including imaging technology.
- Encourage and facilitate collaborative studies within clinical trials networks to develop mechanisms for early identification of individuals at high risk for AIDS-related malignancies. Develop and assess interventional strategies to reduce the risk or prevent the development of malignancies.
- Study the role of immunomodulating agents in the treatment and prevention of AIDS-related tumors.

- Encourage clinical studies of HIV infected individuals with non-AIDS-defining malignancies. Evaluate the impact of therapy on virologic, immunologic, and tumor parameters, and on drug-drug interactions.
- Explore strategies for attenuating or preventing toxicities associated with therapy, and study the effects of such strategies on virologic and immunologic parameters.
- Study the role of *in utero* and long-term exposure to ARVs on the risk of later development of tumors.
- Study populations in resource-limited settings at increased risk of AIDS-related malignancies due to endemic infectious agents (e.g., KSHV/HHV-8) and HPV-associated cervical cancer.

## **OBJECTIVE–J**

**Develop and evaluate strategies for the treatment and prevention of serious manifestations of HIV disease including those prevalent in or unique to international settings.**

(The scientific objectives of H, I, and J are of equal weight.)

## **STRATEGIES**

- Develop and evaluate therapeutic strategies for preventing and treating complications of HIV infection, particularly those complications unique to or prevalent in international settings.
- Develop and evaluate conventional and nonconventional chemopreventive approaches, including those containing quantifiable doses of micronutrients (such as vitamins and trace elements) and macronutrients to delay the development of wasting and other complications of HIV disease.
- Evaluate the safety and efficacy of nonpharmacologic and complementary and alternative medicine approaches, such as exercise, nutrition, and sleep cycles, in the management of HIV disease and its complications.



## **CHAPTER 4**

# Research Related to Specific Populations



**AREA OF EMPHASIS**

# Women and Girls

**SCIENTIFIC OBJECTIVES AND STRATEGIES****OBJECTIVE–A**

Elucidate biologic determinants of HIV transmission and define the mechanisms by which viral, host, and immune factors may influence the process of HIV transmission and acquisition among women and girls across the life cycle.

**STRATEGIES**

- Evaluate HIV transmission and acquisition in relation to viral factors, such as genotype, phenotype (inclusive of drug resistance), clade, viral load, replicative forms, viral fitness, and heterogeneity.
- Identify and characterize cells responsible for viral acquisition and propagation at mucosal surfaces in the oral cavity and the entire reproductive tract (fallopian tubes, uterus, cervix, vagina, vulva) and anal canal.
- Evaluate HIV transmission and acquisition in relation to viral shedding in different mucosal compartments (including semen, cervicovaginal secretions, and saliva).
- Evaluate HIV transmission and acquisition in relation to age, timing, and occurrence of endocrine status changes (premenarche, menarche, postmenarche, pregnancy, premenopause, menopause, and postmenopause); the exogenous use of hormones for contraception, ovulation induction, and hormone replacement should be included.
- Over all age ranges, evaluate HIV transmission and acquisition in relation to normal vaginal (and oral) microflora and various infectious factors, such as sexually transmitted infections (STIs) and preexisting local/systemic infections with other microbes.
- Evaluate HIV transmission and acquisition in relation to host genetic factors that influence susceptibility and resistance to infection.
- Elucidate mechanisms of innate immunity and other cellular factors affecting acquisition of HIV.
- Evaluate HIV transmission and acquisition in relation to other host factors, such as nutrition, nonhormonal contraception use, anatomic/physiologic changes (female circumcision, cervical ectopy, postdysplasia treatment), and localized inflammation secondary to use of intrauterine devices, local vaginal therapies, douches, or vaginal astringents.
- Study the biology of the systemic and mucosal immune system (innate and adaptive) in women and girls and the impact of HIV infection.
- Define how genetic, infectious, and endocrine factors alter local and systemic immune responses and the impact on HIV acquisition and transmission.

- Study the impact of effective antiretroviral therapies (ARTs) on genital tract viral dynamics (including the development of resistance) and vertical and sexual HIV transmission.

**To facilitate the research goals listed above:**

- Develop standardized assays for immune response and viral load, as well as other relevant parameters, in genital tract and oral samples;
- Develop noninvasive procedures for genital tract sampling; and
- Promote studies in animal models to explain host-viral-immune factors involved in HIV transmission and acquisition.

## OBJECTIVE-B

**Study the biology of HIV infection, progression to disease, and development and course of clinical manifestations associated with HIV infection, coinfections, and concomitant conditions among women and girls across the life cycle.**

## STRATEGIES

- Elucidate the unique mechanisms mediating virus-host interactions in HIV disease progression among women and girls.
  - ▶ Evaluate HIV viral dynamics and replication in blood and at the tissue level and immune function among women and girls.
  - ▶ Determine normative values for immune parameters including total lymphocyte number, subset composition, and immune cell turnover and distribution and the impact of HIV infection across the life cycle.
  - ▶ Investigate the role of potential cofactors and mediators of disease progression in both early- and late-stage disease, including hormonal endogenous factors (inclusive of hormonal changes across the life cycle and throughout the menstrual cycle) and exogenous factors (inclusive of hormonal contraception and hormonal replacement therapy); pregnancy; and autoimmune diseases.
  - ▶ Investigate the role of potential cofactors and mediators of disease progression in both early- and late-stage disease, including infectious agents such as hepatitis C virus (HCV) and sexually transmitted infections (STIs); use and abuse of alcohol and other substances; reexposure to different strains of HIV including drug-resistant strains; age; intermittent therapy and monotherapy for perinatal transmission; and genetic factors.
  - ▶ Investigate the role of potential cofactors and mediators of disease progression in both early- and late-stage disease, including nutrition, biological indicators of stress, drug use, and complementary and alternative medicine approaches, including herbal therapies and nutritional supplements.
- Develop approaches for identifying, recruiting, enrolling, and retaining recently exposed and newly HIV infected women and girls for studies on the pathogenesis of HIV infection.
- Elucidate the unique etiologies and pathogenic mechanisms of disease manifestations in HIV infected women and girls.
  - ▶ Investigate HIV- and therapy-associated metabolic and body composition changes that may be operative at various stages of infection and disease, to include changes in fat distribution, bone density, menstrual function, fertility and sexual function, and cardiovascular disease.
  - ▶ Conduct studies on the gynecologic manifestations and identification and treatment of gynecologic disease in HIV infected women and girls.
  - ▶ Elucidate characteristics of opportunistic infections (OIs) and coinfections in HIV infected women and girls.
  - ▶ Elucidate characteristics of HIV-related malignancies, including female-specific cancers.
  - ▶ Investigate the impact of comorbid conditions on HIV-related manifestations in women and girls, including HCV coinfection and autoimmune disease.

- ▶ Elucidate characteristics of neurologic and neuropsychologic manifestations (dementia, changes in cognitive function) of HIV infection/disease in women and girls, including the role of potential cofactors such as substance abuse, mental health disorders, HCV infection, and preexisting neurological conditions.
- ▶ Investigate clinical manifestations related to HIV and HIV-related therapies in pregnant and postpartum women, including toxicity (e.g., lactic acidosis, hyperglycemia) and peripartum/postpartum morbidity in HIV infected women undergoing vaginal or operative delivery.
- Evaluate the impact of HIV and HIV-related therapies on breastfeeding.
- Explore further the role of pharmacogenetic factors as explanations for variations in HIV disease course.

## OBJECTIVE–C

**Conduct and support research to inform the diagnosis, care, and treatment of HIV infected women and girls across the life cycle, including clinical studies of therapeutic interventions.**

## STRATEGIES

- Evaluate innovative and rapid testing strategies in a range of settings to identify HIV infection in women and girls.
- Study the psychosocial consequences of receiving HIV-positive results on women across the lifespan, including during adolescence, during the reproductive years, and during menopausal and postmenopausal stages of life, and the impact on treatment and care decisionmaking.
- Evaluate the impact of antepartum treatment on the natural history of disease and development of viral resistance.
- Enhance efforts to evaluate the efficacy and effectiveness of new and existing therapies and therapeutic regimens across the life cycle, in both treatment-naïve and treatment-experienced women and girls.
- Study factors affecting adherence to HIV therapeutic regimens across the lifespan, and develop and evaluate focused interventions designed to improve adherence to HIV therapy.
- Evaluate the impact of non-HIV therapies and concomitant diseases, including substance abuse and mental disorders, on women's eligibility for participation in clinical trials, access to health care, and utilization of and adherence to treatment.
- Support research and development of clinical trial designs and statistical methodologies to evaluate clinical efficacy and reasons for success or failure of anti-HIV treatments among women and girls, including timing of treatment initiation, treatment interruptions and treatment cycling, treatment in the presence of other comorbid conditions, treatment during pregnancy, and the utility of surrogate markers.
- Conduct research to optimize diagnosis and treatment of comorbidities in women with HIV.
- Evaluate the interaction of mental health therapies and anti-HIV therapies on the course of disease progression.
- Evaluate short- and long-term toxicity, pharmacokinetics, and antiretroviral activity of therapeutic agents in women across the life cycle, including during pregnancy.
- Investigate therapeutic interactions of anti-HIV medications with other medications used by women, including interactions of ARTs with therapies for OIs; therapies for illnesses that affect women specifically, disproportionately or differently from men; hormonal treatments; treatments for substance abuse; and complementary and alternative medicine approaches.
- Evaluate the long-term effects of anti-HIV therapy on morbidity and mortality among girls and women across the life cycle.
- Measure quantity and frequency of alcohol use in treatment and ART pharmacology studies.

## OBJECTIVE-D

**Conduct and support basic and intervention research to address the gender-specific, psychological, behavioral, social, environmental, economic, and cultural dynamics that increase or decrease risk for, and protection from, HIV transmission, acquisition, and disease progression among women and girls across the life cycle.**

## STRATEGIES

- Examine the impact of population-level interventions on HIV acquisition among women and girls, such as social normative behavior changes, programs to increase educational opportunities and economic independence, mass or syndromic approaches to STI control, early diagnosis and treatment of HIV infection and other STIs, use of family planning programs to diagnose and treat STIs, and availability and access to substance abuse treatment.
- Support research across the life cycle that explores the impact of HIV risk perception on sexual activity decisionmaking, including decisions about pregnancy.
- Study how HIV-related risk and protective behaviors might change over time as a function of developmental and life-course events, such as adolescence, childbearing, sexual partnership choice and change, HIV treatment, menopause, and loss of family, social, and economic support.
- Support female-focused intervention research to prevent HIV acquisition through enhanced healthy sexual development and development of protective behaviors across the life course.
- Develop, implement, and evaluate interventions that address partnership issues regarding increased and decreased risk of HIV infection (e.g., dating, relationship violence, power in relationships, drug use, and economic survival sex).
- Develop innovative prevention strategies targeting male partners whose behaviors confer risk of HIV transmission to female partners, particularly in populations/areas with elevated HIV prevalence.
- Develop, implement, and evaluate culturally focused outreach and peer-based HIV prevention interventions that address risk behaviors and related perceptions of risk.
- Develop, implement, and evaluate prevention interventions for populations perceived to be at low risk for HIV infection, such as sexually active middle-aged and older women, college students, those with physical and mental disabilities, bisexual women and girls, women and girls residing in rural areas, Asian/Pacific Islanders, Native Americans, and Alaska Natives.
- Develop, implement, and evaluate culturally focused HIV prevention, treatment, and care interventions targeting populations of women and girls at risk due to vulnerable and/or isolating circumstances (e.g., orphaned, incarcerated, refugees, sexual exploitation, trauma, violence, war, homelessness, runaways, gang membership, alcohol and substance abuse).
- Support research to improve translation of effective culturally focused behavioral and social science-based HIV prevention, treatment, and care interventions to communities and health care and prevention service providers serving women and girls.
- Study the impact of macro events (e.g., natural disasters, trauma, war) on HIV risk for women and girls.
- Support HIV research focused on community-level factors (social, cultural, and gender norms and ideologies) that increase or decrease risk of HIV transmission and acquisition among women and girls.

## OBJECTIVE–E

**Conduct and support basic and intervention research to develop, test, and evaluate safe and effective technologies and products, including vaccines and chemical and physical barrier methods that are appropriate, acceptable, and accessible to women and girls, for preventing transmission and acquisition of HIV.**

## STRATEGIES

- Support the discovery, development, and preclinical evaluation of new, improved, acceptable, effective, and safe chemical and physical barrier methods, including topical microbicides and other methods, to reduce sexual transmission of HIV and STIs among women and girls.
- Support the evaluation of existing chemical and physical barriers to reduce sexual transmission of HIV and STIs among women and girls.
- Support the evaluation of the contraceptive efficacy of chemical and physical barrier methods and how the efficacy affects acceptability for use in HIV prevention.
- Identify populations of women and girls with HIV incidence levels suitable for recruitment into vaccine and other HIV prevention intervention trials.
- Develop and evaluate methods to access, recruit, and retain women and girls who are demographically representative of the populations at risk for HIV infection for preventive intervention studies (women and girls to include racial/ethnic minorities, adolescents, substance users, and the mentally ill).
- Develop and assess the effectiveness of utilizing multiple prevention approaches, both individually and in combination, that may decrease HIV transmission among women and girls.
- Develop and evaluate biomedical and behavioral interventions for managing STIs (including mass treatment or syndromic approaches) as a potential means of preventing HIV transmission and acquisition.
- Investigate candidate vaccines and other biomedical prevention strategies both in human subjects and in animal models of HIV infection with attention to factors particularly relevant to use in women and girls, such as changes in vaginal/cervical epithelium during puberty, hormonal changes during pregnancy, use of contraceptives or hormonal replacement therapy, and presence of selected STIs.
- Study potential effects of candidate vaccine or microbicidal products on the genital tract immune system and their ability to induce inflammatory activity that might compromise the integrity of the mucosal surface of the genital tract and decrease or enhance the inductive ability of vaccines.
- Study the impact of biomedical interventions to prevent mother-to-child transmission, including caesarean section, on maternal morbidity and mortality.
- Support research to improve translation and dissemination and increase adoption of effective HIV prevention technologies by communities and by health care and prevention service providers who serve women and girls.
- Develop and evaluate innovative ways to obtain culturally and age-appropriate fully informed consent for participation in HIV prevention trials, and document critical aspects of informed consent (e.g., procedures, risks, benefits, voluntary nature, confidentiality, etc.).
- Support research to identify barriers to enrolling girls under 18 years of age in HIV prevention trials and to develop strategies for overcoming these barriers, including hard-to-reach populations such as girls living outside of family care, girls involved in the juvenile justice system, and substance abusers.

## **OBJECTIVE-F**

**Conduct and support basic and intervention research on the biological, psychological, social, and economic consequences of HIV/AIDS for infected and affected women and girls.**

## **STRATEGIES**

- Conduct multidisciplinary research to understand the synergistic effects of HIV-related disease progression and premorbid and comorbid clinical and psychosocial conditions affecting women and girls, and the mechanisms underlying these effects; develop interventions to enhance physical and mental health outcomes.
- Develop and evaluate interventions that target HIV-serodiscordant couples to prevent transmission and to promote coping and quality of life.
- Support research to understand the consequences of HIV infection and disease progression on women's and girls' sexual and reproductive health and decisionmaking.
- Support research to improve understanding of fertility intentions and sexual behaviors of women who are or whose partners are HIV-positive, and how fertility intentions are influenced by highly active antiretroviral therapy (HAART); develop and evaluate accessible assisted reproductive technologies designed to assist in meeting fertility goals without HIV transmission.
- Conduct research to examine the consequences of HIV infection and treatment on women's and girls' access to, receipt of, and adherence to treatment for comorbid conditions, including other infectious and noninfectious diseases, substance abuse, and psychiatric illness.
- Examine the association between gender-specific physical and psychosocial consequences of HIV disease and HIV-related treatment initiation and maintenance.
- Develop and evaluate interventions to reduce adverse psychological, social, and economic consequences for women and girls infected or affected by HIV/AIDS, such as educational and economic opportunities, access to treatment and care, and prevention of violence and abuse.
- Conduct basic research to understand the dynamics of gender-specific stigma/discrimination associated with HIV/AIDS and to inform the development of structural interventions to reduce HIV/AIDS-associated stigma.

**OBJECTIVE–G**

**Identify and address the factors that influence women’s and girls’ access to and experience of HIV/AIDS-related research, care, support, treatment, and prevention services.**

**STRATEGIES**

- Support research to understand how the organization, financing, management, access, delivery, cost-effectiveness, and cost-utility of health care, reproductive health, family planning, and social services affect HIV risk behaviors, HIV transmission, and access to appropriate HIV care, support, treatment, and prevention services.
- Support research to develop effective strategies for the linkage, coordination, and integration of HIV care, support, treatment, and prevention services with primary medical care; drug, alcohol, and mental health treatment; STI services; reproductive health and family planning services; educational services; and community social services.
- Conduct research to examine transition of HIV/AIDS care across the lifespan, from pediatric to adolescent to adult care, and from adult to geriatric care, and develop interventions to optimize transition of care.
- Support research to understand the impact of policy and policy change—such as health care, health sector reform, health care financing systems, legislation, and regulations—on the delivery and utilization of HIV-related services, HIV risk behavior and transmission, and HIV/AIDS disease outcomes among women and girls.
- Encourage multidisciplinary research to identify unmet needs and elucidate barriers for women and girls to achieving optimal HIV care, support, treatment, and prevention services.
- Support research to study and address factors that influence the full participation of women and girls in HIV/AIDS-related research, including clinical trials for novel therapeutics and vaccines.
- Support research on effective strategies for disseminating products, findings, and information from HIV/AIDS-related research to women, girls, their communities, and policymakers.

## **OBJECTIVE–H**

**Conduct and support research, training, and education on ethical issues specifically affecting women and girls in HIV/AIDS-related clinical, behavioral, epidemiological, and health care services research in different cultural settings.**

## **STRATEGIES**

- Develop and evaluate efforts to educate women and girls who are potential trial participants about ethical and human rights issues in human research in advance of recruitment, with the goal of obtaining fully informed and free consent.
- Investigate the unintended consequences of policies and practices (including research practices) that provide special benefits to HIV infected—as compared to uninfected and unaffected—women and girls (e.g., preferential treatment, health care benefits, access to medications, social services). Conduct research to examine and determine the contexts and factors that influence when the consent process is fully voluntary and is an informed aspect of the consent process.
- Investigate unintended harms and benefits that may accrue to women and girls, their families, and their communities as a result of participation in research studies.
- Examine the ethical risks and benefits of studies that involve treatment versus observation of women and girls.
- Investigate the ethical impact within a community of studies in which clinical trials provide the only access to therapeutics for women and girls.
- Assess potential negative and beneficial consequences for women and girls of conducting community-level epidemiological research.
- Study the ethical issues related to diagnostic and therapeutic strategies during pregnancy and lactation.
- Study the ethical issues related to breastfeeding and its alternatives.
- Study the ethical issues related to participation of women and girls in clinical trials.

## AREA OF EMPHASIS

# Racial and Ethnic Minorities

## SCIENTIFIC OBJECTIVES AND STRATEGIES

### OBJECTIVE–A

Examine sociocultural and structural determinants, social structures, and health systems that enhance, sustain, and/or perpetuate health disparities.

### STRATEGIES

- Emphasize basic research and its clinical application to determine the impact of culture, race, and gender upon the response to HIV infection and treatment.
- Explore the effect of poverty, limited education, and health illiteracy, as well as acculturation, language fluency, and access to services, upon the ongoing disparity in HIV infection among immigrants.
- Examine the influence of race/ethnicity and gender, independently and in combination, upon social norms and cultural contexts that affect HIV transmission risk behaviors, as well as HIV disease progression.
- Design and conduct studies that determine the factors that promote and/or impede early access to care and treatment, with attention to individual and health care system factors.
- Develop and enforce mechanisms that share information gathered from trial data with the communities that participated in NIH-funded programs, allowing the collection of such data.
- Encourage, through specific funding initiatives, studies to examine the impact of traumatic stressors upon indigenous domestic populations, including Native Americans and Alaska Natives, such as acculturative stress and intergenerational trauma, upon HIV risk behaviors and HIV health-care-seeking behavior.
- Examine the influence of stigma, racism, homophobia, and racial and cultural stereotypes among health care providers and health care systems (including infrastructure) upon racial and ethnic minority community HIV care access, as well as provision of HIV treatment.

## **OBJECTIVE–B**

**Identify and examine the health care, social systems, and structural barriers that promote and sustain the health disparity in HIV infection among racial and ethnic minorities.**

## **STRATEGIES**

- Promote and sustain interagency research to:
  - ▶ Determine the impact of the criminal justice system in increasing the risk of HIV transmission among racial and ethnic minorities;
  - ▶ Determine the disease burden accruing within the criminal justice system and the effect of this disease burden upon the health care systems and infrastructure within racial and ethnic minority communities; and
  - ▶ Determine the impact of reentry of HIV infected individuals from prison to the community upon HIV care provision, as well as antiretroviral drug resistance.
- Determine the impact of combined economic and educational disparities upon the health outcomes of racial and ethnic minorities with HIV infection.
- Examine and evaluate the role of health care disparities and public policy factors in sustaining the disparities in the health outcomes of racial and ethnic minorities with HIV infection.
- Determine the impact of structural factors within health-related organizations, such as insurance status and institutional racism, upon when racial and ethnic minorities present for HIV-related care and its impact upon disease progression.
- Encourage, through targeted funding, interdisciplinary research that develops and tests interventions designed to reduce/eliminate structural factors that impede access to HIV-related care.
- Support studies that examine and quantify the potential impact of incorporating HIV-related services into existing services for reproductive health, family planning, and sexually transmitted infection already placed within racial and ethnic minority communities. This would include the impact upon not only HIV prevention and infections averted, but also HIV detection, care, and community awareness.

## OBJECTIVE–C

**Enhance and expand the capacity for NIH-funded HIV research by underrepresented minority investigators, institutions, and communities, especially Native American and Alaska Native. Minority is defined as any racial or ethnic group other than Caucasian in the United States.**

## STRATEGIES

### For the investigator:

- Promote and expand predoctoral opportunities for the development of minority investigators.
- Establish a national mentoring network for the development and retention of racial and ethnic minority investigators in HIV/AIDS research.
- Conduct a review through the Office of Extramural Research, in response to the National Research Council report, to determine the number of minority scientists produced as a result of existing NIH programs (such as the K award, minority biomedical research supplements) to support the transition from trainee to independent investigator, with the goal of enhancing and expanding successful programs.
- Through existing funding mechanisms, provide incentives and support for senior investigators to identify, develop, and mentor racial and ethnic minority investigators in culturally and contextually appropriate HIV/AIDS research domestically and internationally.
- Through existing funding mechanisms, provide incentives for the development, recruitment, and retention of intramural and extramural racial and ethnic minority investigators, including the provision of scholarship support to attend scientific meetings.
- Review existing programs designed to increase the awareness of underrepresented racial and ethnic minority investigators of NIH funding mechanisms for HIV/AIDS research, enhancing those programs that are successful and eliminating those that are not.
- Recreate scientific review panels at the Center for Scientific Review and the Institutes, as current panels reflect neither the demographics of the epidemic nor the populations affected. Annual reporting of the increases in racial and ethnic minority participation on review panels, including ad hoc panels, should be made to the Director of the Office of AIDS Research.

### For the institution:

- Increase the number of minority and majority institutional partnerships with shared research interests for research program and infrastructure development, building upon successful existing models such as the National Center for Research Resources.
- Utilize existing funding support to minority-serving and minority-predominant institutions for the development of an HIV/AIDS research agenda, including an assessment of needs.
- Utilize existing funding mechanisms targeted to minority institutions to ensure training and development of sufficient personnel for the successful conduct of HIV/AIDS research.
- Enhance community-academic partnerships by requesting a plan for research development as part of the peer-reviewed application, documenting bidirectional collaboration.

- Foster coalitions and partnership-building with other institutions, across Department of Health and Human Services (DHHS) agencies and stakeholders, to strengthen strategic collaborative efforts to address HIV/AIDS research issues in racial and ethnic minority communities.
- Improve basic science capacity at minority-predominant and minority-serving institutions (including tribal entities) through mentored training awards, infrastructure development, and majority-minority institutional partnerships and collaborations.

**For the community:**

- Increase minority participation on community advisory boards for HIV research to reflect their current incidence and trends in the epidemic.
- Include community consultations in NIH-funded extramural research from study development to the dissemination of study results.
- Share study results with participants promptly through existing information dissemination mechanisms as well as through community organizations/research partners.
- Fund community-based and community-driven participatory research to facilitate bidirectional transfer of knowledge and observations of interest to both the community and the investigator(s).

## OBJECTIVE-D

**Conduct HIV research that includes numbers of racial and ethnic minorities that reflect not only the current domestic HIV/AIDS prevalence, but also emerging incidence trajectories in minority subgroups.**

## STRATEGIES

- Require that clinical trials be appropriately powered to conduct subgroup analyses exploring the potential for differential responses to treatment, metabolic toxicities, drug adverse events, and immune responses in racial and ethnic minorities.
- Facilitate through funding incentives at both the investigator and the research institution levels, academic-community partnerships to enhance clinical trial recruitment and retention of racial and ethnic minorities.
- Advance the awareness and understanding of the ethics of clinical research, as well as the protections required for research participants, in racial and ethnic minority communities through innovative approaches in partnership with the community-based organizations that serve these communities and neighborhood key opinion leaders.
- Examine the impact of exclusion criteria, to determine if any particular population or populations are more frequently eliminated. Propose strategies to protect such populations in order to facilitate their participation in clinical research.
- Evaluate the effects of HIV infection by age and gender upon the physiologic, immunologic, hormonal, and neuropsychological development of racial and ethnic minority adolescents for potential therapeutic interventions.
- Develop, test, and support creative clinical research methodologies that examine prospectively racial/ethnic/gender/sexual orientation differences in transmission, pathophysiology, and treatment outcomes.
- Determine the impact of race-related factors in understudied indigenous populations, including Native Americans, Alaska Natives, Pacific Islanders, and Native Hawaiians.
- Identify the factors that influence HIV transmission among racial and ethnic minorities.
- Examine the impact of alcohol, drug use, and chronic medical and neuropsychiatric comorbidities on the success or failure of HIV clinical interventions and HIV disease progression in racial and ethnic minorities.
- Continue exploration of proteomics and genomics to determine the individual and combined effects of race, gender, and age upon immune response and response to treatment.
- Advance the study of the biology of HIV infection among racial and ethnic minorities by:
  - ▶ Evaluating the effect, if any, of race/ethnicity and gender upon immune dysfunction and the development of opportunistic infection;
  - ▶ Determining the effect of race/ethnicity and gender upon p-glycoproteins and their role in the individual response to HIV therapy and the development of HIV drug resistance; and
  - ▶ Exploring the role of preexisting health conditions disproportionately found in racial and ethnic minorities, such as cardiovascular disease, diabetes, and hepatitis, upon HIV disease course and progression.
- Develop, test, and promote successful strategies for linking community organizations with NIH research performance sites through the use of Internet resources, such as [AIDSinfo.nih.gov](http://AIDSinfo.nih.gov).

## **OBJECTIVE-E**

**Explore the effect of HIV infection as a chronic disease with long-term consequences upon racial and ethnic minority individuals, as well as their communities.**

## **STRATEGIES**

- Determine the impact of preexisting and coexisting disorders such as alcohol use and abuse, substance abuse, hepatic infections, sexually transmitted infections, and mental health disorders upon HIV infection and progression, to develop and implement successful intervention strategies.
- Fund research that explores factors that prevent chronic HIV disease, including:
  - ▶ The role of extended and nuclear family and caregivers;
  - ▶ The role of traditional and nontraditional organizations upon social structure and norms;
  - ▶ The role of peer and social networks; and
  - ▶ Individual, as well as community, interface with health care delivery systems.
- Study the impact of alcohol, substance abuse, and mental health treatment as an approach to HIV prevention.
- Expand research to identify specific points for intervention in racial and ethnic minority communities to prevent the long-term sequelae of sexually transmitted and HIV infections by:
  - ▶ Identifying the barriers to participation in microbicide and vaccine trials among racial and ethnic minorities, and testing interventions to overcome these barriers;
  - ▶ Enhancing research on the potential impact of vaccines and microbicides upon HIV transmission among racial and ethnic minorities; and
  - ▶ Promoting research to identify successful interventions to promote access to, as well as retention in, HIV treatment.
- Promote research on HIV infection among older racial and ethnic minority individuals with and without preexisting chronic conditions, and the impact of overall general health status upon HIV transmission in these individuals.
- Determine the impact of HIV infection upon functional expression, including quality of life, function, functional status, and the aging process.

**OBJECTIVE-F**

**Develop and test innovative research, models, methods, and measures to accurately assess risk behavior.**

**STRATEGIES**

- Develop, pilot, test, and evaluate new measures of HIV risk behavior that investigate the influences of culture and context on the behaviors of racial and ethnic minorities.
- Develop new models of HIV behavioral interventions that incorporate common stressors and experiences for racial and ethnic minorities, including racism, acculturation, and stigmatization.
- Develop new models of HIV behavioral interventions that take into account the interrelated risks associated with substance abuse, socioeconomic status, trauma, and cultural and gender identity.
- Develop novel sampling methods to enhance the representation of racial and ethnic minorities in clinical research, with attention to sampling adequately from indigenous populations.
- Fund through specific announcements the development and testing of new sampling methodologies in racial and ethnic minority communities.
- Identify resiliency and protective factors found in racial and ethnic minority communities, and test them for their impact upon decreasing HIV transmission.
- Validate existing measures for language translation accuracy and for cultural and linguistic equivalents for each of the racial and ethnic minority communities in which they are to be used.
- Identify sampling methods and intervention models that measure racial and ethnic minority subpopulation differences in behavioral risks and outcomes.
- Fund the development and standardization of assessment tools that are designed for the racial and ethnic minority community in which they are to be used.
- Study HIV risk behaviors of underrepresented racial and ethnic minorities, such as Native Americans, Alaska Natives, and Asian Pacific Islanders, including the role of intergenerational trauma and acculturative stress.

## **OBJECTIVE–G**

**Identify factors that contribute to delay in the diagnosis of HIV/AIDS in racial and ethnic minority communities and hence contribute to delays in treatment. Investigate public health, community, and individual approaches that will facilitate earlier identification of HIV infection, as well as prompt access to treatment and care.**

## **STRATEGIES**

- Determine the effect of stigma (expressed and perceived), race, ethnicity, gender, and sexual orientation upon delayed testing for HIV infection, delayed treatment, and adherence to treatment.
- Identify factors at the individual, societal, and community level that promote HIV testing, treatment, and adherence; develop interventions to determine their effectiveness in racial and ethnic minority communities.
- Study the impact of provider decisionmaking, as well as provider-patient interactions, that negatively and positively affect the decision to consent to HIV testing and treatment in racial and ethnic minorities.
- Define the role and impact of health beliefs and prior experiences with the health care system upon HIV testing, treatment acceptance, and treatment adherence in racial and ethnic minorities.
- Explore the use of complementary and alternative therapies in racial and ethnic minority communities as an alternative to seeking care in conventional health settings due to stigma, fear, or mistrust.
- Maintain research upon the impact of complementary and alternative therapies upon treatment adherence for HIV infection, symptom relief, and the complications of HIV infection.
- Fund studies of community-based multilevel interventions to promote HIV testing, care seeking, and treatment.

## AREA OF EMPHASIS

# Research in International Settings

## SCIENTIFIC OBJECTIVES AND STRATEGIES

### OBJECTIVE–A

Develop a sustainable, collaborative research environment by utilizing and enhancing in-country capacity.

(The scientific objectives of A and B are of equal weight and serve as a prerequisite foundation for objectives C through I.)

## STRATEGIES

### Site Development

- Encourage the integration of NIH-supported research programs being conducted in resource-limited countries by U.S. researchers with established in-country programs, including collaboration with local investigators on strategic planning for research.
- Assess existing sites and, as needed, further develop sustainable, existing in-country sites, or establish new international research sites as rapidly as possible to address urgent and emerging scientific opportunities.
- Enhance capacity for the conduct of basic and applied prevention and treatment research, with emphasis on maintaining both Good Laboratory Practice (GLP) and Good Clinical Practice (GCP) requirements for large-scale clinical trials, through:
  - ▶ strengthening laboratory capacity with appropriate quality assurance and training;
  - ▶ developing clinical capabilities through research training and “hands-on” research experiences;
  - ▶ developing affordable alternatives to viral load and CD4+ cell counts and expensive laboratory monitoring for treatment efficacy and toxicity;
  - ▶ supporting the analysis of scientific and research-based international databases and developing common laboratory information management systems;
  - ▶ enhancing data collection and analysis capabilities;
  - ▶ addressing barriers in maintaining repositories of biological samples in resource-constrained countries;
  - ▶ developing and testing strategies for recruitment and retention of participants in prevention, treatment, and care studies;
  - ▶ enhancing the ability to ensure protection for human subjects involved in research and the ethical conduct of research, including informed consent and issues specific to women and children;
  - ▶ enhancing mechanisms for information exchange among investigators, including enhanced electronic communication;

- ▶ conducting research on how to scale up from pilot projects and/or early Phase I and II trials to large research studies, including Phase III trials, and on how to apply research findings to the general population;
  - ▶ strengthening community advisory boards to participate in the development and design of clinical trials and other research, as well as in the translation of research results into programs and policies;
  - ▶ strengthening financial management, accounting, and business office practices; and
  - ▶ strengthening library services and access to scientific resources.
- Build global capacity to conduct operational research, including outcome and cost-effectiveness studies and modeling, to rapidly address emerging priorities in prevention, treatment, and care.
  - Conduct studies on incidence and feasibility in order to identify sites suitable for the conduct of efficacy trials of HIV prevention, treatment, and care interventions.
  - Develop and provide training at international sites conducting vaccine studies on the role and responsibilities of an institutional biosafety committee (IBC).
  - Develop regional approaches to research (e.g., through regional meetings and training) to enhance communication and to address common issues and needs among countries in a region.

#### **Collaboration and Coordination**

- Ensure that foreign investigators are full and equal partners with U.S. scientists in the design, conduct, and analyses of clinical studies.
- Enhance coordination of NIH international AIDS research, particularly when multiple projects are active in the same country and/or region.
- Encourage the continued development of research collaborations between international and U.S. investigators, ensuring project relevance to strategic planning at the local level, to maximize the research effort in resource-limited settings; and encourage U.S. researchers to participate at the developing country research site to better understand the challenges of conducting research and providing care and services in such settings.
- Provide assistance to foreign collaborators in addressing regulatory issues and special oversight mechanisms.
- Coordinate with other U.S. Government agencies, including the Centers for Disease Control and Prevention (CDC), the U.S. Agency for International Development (USAID), the Health Resources and Services Administration (HRSA), and the State Department.
- Work with foreign governments, international organizations (e.g., the World Health Organization [WHO], with particular emphasis on coordinating research and research infrastructure development with WHO's 3x5 Program), the Global Fund for AIDS, Tuberculosis, and Malaria (GFATM), nongovernmental organization (NGOs), private industry, foundations, and alliances (e.g., Global HIV/AIDS Vaccine Enterprise) to help identify priorities, gain efficiencies, and reduce overlap in the development and testing of vaccines, microbicides, drugs, and other prevention, care, and treatment strategies, including behavioral interventions.
- Explore collaborations with reputable indigenous health providers to better understand their roles and practices in HIV/AIDS care and prevention; to facilitate their involvement as partners and indigenous health professionals in global HIV/AIDS research, care, and prevention; and to identify practices that may add value in treating and preventing diseases in diverse geographical settings.

## Ethical Issues

- Ensure that research projects are designed to benefit the countries in which the research is being conducted.
- Enhance the capability of institutions in resource-limited settings to conduct independent scientific and ethical reviews.
- Ensure education/cross-fertilization between resource-limited countries' ethical review committees and U.S. institutional review boards (IRBs), and educate U.S. IRBs about cultural issues in developing countries.
- Ensure the participation of local researchers/scientists, communities, NGOs, and governments in the development of research protocols.
- Ensure that ethical challenges in both research and the implementation of research results in resource-limited settings are clearly described and addressed in grant proposals.
- Implement the *Guidance for Addressing the Provision of Antiretroviral Treatment for Trial Participants Following their Completion of NIH-Funded HIV Antiretroviral Treatment Trials in Developing Countries*.
- Ensure confidentiality of information about HIV infected individuals, including information on individuals in treatment for substance abuse.
- Ensure that ethical review mechanisms, such as informed consent forms, are relevant and appropriate to the country where the research is conducted and are placed in cultural context.
- Conduct workshops on ethical principles and their implementation in research, encouraging countries to develop their own set of ethical guidelines and procedures, to include the principles of respect for persons, beneficence, and justice, and the application of informed consent, assessment of risks and benefits, and selection of subjects.
- Encourage in-country scientists and leaders to work closely with local journalists to foster understanding of science, the role of research, and relevant ethical issues.
- Conduct research designed to identify ways to improve the application of ethical principles in the conduct of research in varied cultural settings, including a focus on informed consent.

## Technology Transfer and Translation of Research Results

- Ensure results are provided to and understood by participants and staff involved in research studies and available for their use.
- Develop distance learning approaches to enhance communication of research results and translation into prevention, treatment, and care programs.
- Provide improved access to information concerning treatment and prevention guidelines and the results of research through enhanced information technology.
- Facilitate development of locally appropriate and acceptable HIV prevention and treatment guidelines, by including behavioral, basic, epidemiological, and clinical research findings.
- Transfer clinical, laboratory, and public health technologies that may be sustained and used for implementation of prevention, symptom management, clinical training, and patient care programs once research studies are completed.

## **OBJECTIVE-B**

**Develop an in-country community of investigators committed to a culture of leadership in research through providing sustainable mentoring for junior investigators and career development opportunities for mid-career and senior investigators.**

**(The scientific objectives of A and B are of equal weight and serve as a prerequisite foundation for objectives C through I.)**

## **STRATEGIES**

- Ensure the leadership role of in-country investigators and policy-level individuals in countries where studies take place by involving them in all stages of the research, including conceptualization of the research question, study design, development of protocols, study implementation and collection of data, data analysis, publication and presentation of research results, and interaction with the media.
- Develop in-country training partnerships, and support “south-to-south” training to enable investigators to obtain training appropriate for the areas in which they will work by (1) developing a cadre of in-country scientific professionals, and (2) providing opportunities to enable trained investigators returning to their home countries to serve as training resources for others.
- Continue to support training, both in-country and in the United States, of clinicians (physicians and nonphysician professionals, e.g., nurses, midwives, etc.), public health professionals, and scientists from developing nations to enhance the conduct of research on HIV, AIDS, sexually transmitted infections (STIs), and other HIV-related coinfections and malignancies, including research training related to (1) treatment and care, (2) clinical trials of therapeutic strategies for HIV and endemic coinfections, (3) development and testing of vaccine candidates, (4) impact of alcohol and other substance abuse/dependence on HIV transmission, (5) reproductive health, including microbicides, (6) disease progression, (7) prevention of mother-to-child transmission (MTCT), and (8) other biomedical, social, and behavioral prevention research.
- Provide training in data management and analysis for in-country research personnel.
- Provide training to enable in-country researchers to meet the requirements of GCP and GLP, including training and maintenance of medical records.
- Provide training in the ethical conduct of research, including informed consent and other topics related to the protection of human subjects.
- Provide training in all aspects of grantsmanship, including preparation of grant proposals, grants management, reporting requirements, research administration, and fiscal accounting.
- Provide training to ensure that clinicians and other health care workers are knowledgeable about infection control principles and can implement proper procedures in resource-constrained countries.
- Enhance training in translational, operational, and health services research.

**OBJECTIVE–C**

Conduct studies to identify effective structural and policy interventions to address the HIV/AIDS epidemic.

(The scientific objectives of C through I are of equal weight.)

**STRATEGIES**

- Determine barriers and facilitators to acceptance of voluntary counseling and testing (VCT), and develop better health system-level approaches to the provision of VCT, including:
  - ▶ assess new VCT approaches for cost-effectiveness and impact on reducing risk from sexual behavior and drug use in settings with varying levels of HIV seroprevalence; and
  - ▶ change community norms for seeking VCT that encourage knowledge of one's status, help mitigate social harm, and reduce HIV stigma.
- Identify the most effective and sustainable ways for schools, leisure locations, and worksites to support behavior change interventions.
- Investigate the effectiveness of community-based and community-level HIV prevention programs, including prevention education and strategies to evaluate, replicate, and extend effective behavioral interventions.
- Ensure that all research is conducted in culturally appropriate content, form, and format.
- Evaluate the effectiveness of expanded access to needle and syringe exchange programs and the policy-level changes necessary to implement such expanded interventions.

## **OBJECTIVE–D**

**Support HIV/AIDS research to develop interventions that address the issues of gender, power relationships, stigma, and discrimination.**

**(The scientific objectives of C through I are of equal weight.)**

## **STRATEGIES**

- Conduct research on sex and gender differences in access and use of prevention and care services.
- Study gender-related social and behavioral factors affecting acquisition of HIV infection.
- Study gender-related biological factors affecting susceptibility to HIV infection, including the use of hormonal contraceptives and the presence of gender-specific conditions, such as human papillomavirus (HPV) infection and cervical cancer.
- Study the psychological impact of HIV infection in women, including their role as heads of households and/or caregivers, the impact of additional pregnancies, and family support.
- Develop interventions to mitigate the negative social consequences of HIV infection related to AIDS stigma and discrimination, with particular emphasis on children infected with or affected by HIV (i.e., AIDS orphans).
- Evaluate laws and legal policies at the local, State, and national levels that operate to sustain stigma.
- Design and evaluate strategies to reduce stigma and discrimination and increase willingness of individuals to enter into voluntary counseling and testing; identify, accept, and implement alternative infant feeding practices; and receive and adhere to antiretroviral therapy (ART) regimens.

**OBJECTIVE-E**

**Study the significance of interactions among individuals in various risk groups, and develop and evaluate interventions and strategies to prevent HIV risk behaviors in social settings and high-risk networks.**

(The scientific objectives of C through I are of equal weight.)

**STRATEGIES**

- Develop sustainable behavioral and community-specific interventions to address multiple risk factors.
- Conduct research to integrate the multiple components of diverse issues of sexuality, alcohol and other substance use, and mental health into HIV prevention programs.
- Develop and test prevention strategies that address relationships between noninjection drug use and sexual transmission.
- Develop interventions targeted to both HIV infected and HIV-uninfected individuals that are designed to appeal to specific populations such as women, men, adolescents, and the military.
- Develop and test prevention interventions to be used in the family context to prevent risky behavior and HIV acquisition and transmission by its members.
- Study the role of migration in the spread of the HIV epidemic in diverse geographical regions.
- Conduct studies to develop interventions at multiple levels (individual, couple, group, society) that reflect and address regional aspects of the epidemic.
- Investigate the role of alcohol and other commonly used psychoactive substances in promoting or facilitating high-risk sexual behaviors that reduce the efficacy of prevention strategies.
- Define sexual and drug use behaviors and their predictors in HIV infected populations, and design and test interventions to reduce the risk of HIV transmission.
- Determine the factors involved in the social networks of injection and noninjection drug users and heavy drinkers that influence the rates and patterns of HIV infection, and design prevention programs based on these results.
- Study how alcohol use, including systems of payment using alcohol, affects increases in HIV risk in seasonal and nonseasonal migrant populations.
- Conduct studies to identify sustainable interventions at the levels of the individual, social network, community, and society to prevent HIV and hepatitis C virus (HCV) transmission as a result of high-risk sexual activity and/or drug use practices.
- Devise strategies to prevent initiation of drug use, alcohol dependence, and transition to riskier drug practices, such as initiating drug injection and sharing of injection equipment.

## **OBJECTIVE-F**

**Develop and evaluate biomedical prevention interventions and strategies.**

(The scientific objectives of C through I are of equal weight.)

## **STRATEGIES**

- Evaluate techniques for detection of acute HIV infection, and study the effects of early identification of potential HIV transmitters on HIV infection spread in different settings.
- Utilize population-based studies to examine basic scientific questions about HIV infection, mechanisms of transmission, and host responses, including viral evolution, viral diversity, human immunology, and mucosal factors in transmission.
- Study the risk of transmission of drug-resistant strains of HIV.

### **Vaccine Development**

- Continue the accelerated efforts toward development of vaccine candidates suitable for use around the world, and foster the development of vaccines to optimize characteristics appropriate for broad international use, including candidates exhibiting low cost with ease of production and administration, as well as stability.
- Define immune approaches that will provide specific and sustained protection against HIV transmission; develop the products necessary to achieve these goals; and develop the capacity to evaluate their safety in human subjects.
- Provide a scientific knowledge base (incidence, viral subtypes, major histocompatibility [MHC] types, natural history) to guide decisionmaking regarding the need for clinical trials in international sites and to conduct trials in these sites and communities according to the highest clinical and ethical standards.
- Identify suitable populations of adults and children to enroll in clinical trials of candidate vaccines.
- Conduct Phase I, Phase II, and Phase III clinical trials for safety, immunogenicity, and efficacy with suitable candidate vaccines in domestic and international settings.
- Enlist the participation of local community representatives in the development of appropriate trial protocols, as well as responsive mechanisms to inform and educate the participating individuals; establish networks within the community that will effectively address the social and medical concerns of the participants; and establish mechanisms to provide ongoing information and open discussions concerning the scientific rationale of the study.
- Examine relevant behavioral issues related to the conduct of vaccine research and its acceptability in diverse populations.
- Conduct research on the social and economic impact of vaccines and their cost-effectiveness.

### **Microbicides and Barriers**

- Discover and develop candidate microbicides to prevent sexual transmission.
- Determine the efficacy and use of prevention interventions, including microbicides and other physical/chemical barrier methods, and determine the factors affecting their use.

- Determine the cost-effectiveness of microbicides and other physical/chemical barrier methods in limiting transmission and curtailing the expansion of the epidemic.

### STIs and Other Diseases

- Determine the efficacy and cost-effectiveness of syndromic management of STIs among HIV infected individuals to prevent HIV transmission.
- Improve clinical management of viral STIs in HIV infected individuals, emphasizing coinfections with herpes simplex virus (HSV)-2 and HPV.
- Identify gender-related biological factors affecting susceptibility to HIV infection, including the use of hormonal contraceptives and the presence of gender-specific conditions such as HPV infection and cervical cancer.
- Examine the impact of coinfection with other endemic diseases on HIV disease, including the risk of acquiring and/or transmitting HIV infection and disease progression. Determine the role of sexual transmission of HCV in coinfection with HIV.

### Substance Abuse

- Evaluate innovative, culturally relevant, contextually appropriate alcohol and drug abuse treatment programs for their utility as HIV and HCV prevention approaches in different international settings.
- Develop approaches for drug and alcohol abuse programs among HIV- and HCV-coinfected patients to improve adherence with drug/alcohol treatment strategies.
- Develop innovative strategies for identifying “hidden populations” of young drug users and out-of-treatment drug users.

### MTCT: Considerations for the Mother, Infant, and Child

- Develop safe, effective, feasible, and conveniently administered strategies to interrupt MTCT, using interventions that are affordable and can be implemented in resource-constrained countries, including specific strategies to prevent postnatal transmission of HIV through breast milk by providing prophylaxis to the infant, mother, or both during the lactation period.
- Develop and evaluate strategies for reducing the risk of MTCT, providing safe ART to pregnant women, and assessing the effects of variable-length combination ART to HIV infected women on both MTCT and the women’s own health, including the impact on subsequent pregnancies.
- Study the effects of antiretroviral (ARV) regimens used for maternal health indications on the risk of MTCT (including postnatal transmission through breast milk) and other outcomes, including pregnancy outcomes.
- Investigate the mechanisms and timing of MTCT (*in utero*, intrapartum, and postpartum via breast milk) to facilitate and develop targeted drugs/strategies to further decrease MTCT or provide alternatives to currently identified effective strategies.
- Further identify cost-effective, nondrug regimens for preventing MTCT, such as research on infant feeding, including:
  - ▶ acceptability of safe breastfeeding alternatives;

- ▶ impact of the use of breast milk alternatives on morbidity and mortality of both the mother and infant; and
- ▶ role of exclusive breastfeeding.
- Conduct studies to evaluate and reduce short- and long-term toxicities of ARVs in women during pregnancy and in their offspring who were perinatally exposed.
- Investigate the unique immune status of pregnant women and their infants and develop immune interventions to interrupt HIV transmission.
- Examine the role of maternal and infant nutrition during the peripartum and postpartum periods in reducing morbidity and mortality in HIV infected mothers and their infants and in reducing MTCT.
- Study the impact of the health status of HIV infected mothers on the survivability of both HIV infected and HIV-uninfected children.
- Study the impact of breastfeeding on the health status of HIV infected mothers.
- Investigate the risk of MTCT when maternal HIV infection is acquired during pregnancy, including:
  - ▶ impact of maternal acute infection on *in utero* risk of MTCT;
  - ▶ impact of maternal acute infection on established interventions for preventing MTCT; and
  - ▶ development of public health approaches for detecting or reducing maternal incident infection during pregnancy.

**OBJECTIVE–G**

**Develop and evaluate the most effective, setting-specific strategies for care and treatment of HIV-related conditions and their sequelae among HIV infected and affected children, adolescents, and adults.**

(The scientific objectives of C through I are of equal weight.)

**STRATEGIES**

- Determine affordable, safe, and effective ARV regimens, including timing of initiation and durability of initial treatment.
- Evaluate and monitor treatment efficacy, adherence, side effects, and toxicity of ARVs and opportunistic infections (OIs) prophylaxis medications in adult, adolescent, and pediatric populations in resource-constrained settings.
- Collaborate with clinicians from resource-limited countries to recruit and retain acute and early HIV infection cases in treatment research programs.
- Determine the role of pharmacogenetics/pharmacokinetics and identify appropriate ARVs that can be used in specific populations (e.g., adults, children, and adolescents) in resource-constrained countries.
- Determine the efficacy of ARV regimens on various clades prevalent around the world.
- Investigate interactions of ARVs with alcohol, drugs of abuse, or medications used for the treatment of substance abuse.
- Characterize the clinical course of HIV infection in diverse geographic settings.
- Identify conditions that emerge as a consequence of ART and longer survival, such as malignancies, neurological and neuropsychological conditions, and metabolic and nutritional dysfunctions.
- Support the long-term followup of children exposed to ART *in utero* and/or postpartum to evaluate possible late effects of ARV exposure.
- Assess the impact of nutritional status and nutritional interventions on patient survival and the efficacy and tolerability of ART, including measuring the rate of immune system deterioration.
- Develop and evaluate care models, such as family models of care, and enhance interdependent care services that integrate AIDS care into existing programs, such as tuberculosis (TB) control programs, alcohol and other substance abuse/dependence treatment programs, and maternal and child health services, to avoid duplication of efforts.
- Develop and evaluate strategies to initiate and provide care to targeted groups of individuals such as health care workers, security forces, and teachers.
- Conduct community-based studies that assess the impact of community mobilization on treatment success.
- Examine the effectiveness of a variety of approaches to the administration of therapy (e.g., directly observed therapy or directly delivered therapy).
- Conduct studies, including clinical trials and operational research, on the quality of treatment, its effectiveness, and its efficacy.

- Develop and test strategies to support adherence in adults and children to medication regimens to enhance therapeutic outcomes and limit the development of drug resistance.
- Investigate the impact of alcohol abuse, drug abuse, and other associated comorbid conditions on HIV disease progression, adherence to treatment regimens, and clinical outcomes.
- Develop and evaluate suitable, sustainable approaches for diagnosis of HIV infection, monitoring treatment safety and efficacy, side effects, and toxicities, with particular emphasis on finding affordable technologies to measure CD4+ cell counts and HIV load, as well as suitable alternatives.
- Assess the cost-effectiveness of ARVs in resource-limited countries and determine the minimal level of ARV resistance monitoring necessary and the methods to be used for such monitoring.

**OBJECTIVE–H**

**Study the interactions between HIV infection and endemic diseases, and develop strategies to optimize diagnosis, treatment, and care.**

(The scientific objectives of C through I are of equal weight.)

**STRATEGIES**

- Examine the role of coinfection with other endemic diseases and their treatment in modulating HIV infection or disease, including risk of acquiring and/or transmitting HIV infection and disease progression.
- Investigate the impact of coinfections with other endemic diseases and their treatment on the use of ART.
- Determine the impact of ART on susceptibility to infection with endemic diseases and on their natural history.
- Determine the impact of ART on the efficacy of treatment and prophylaxis for other endemic diseases.
- Investigate drug-drug interactions of ARVs and drugs used to prevent and treat endemic infections.
- Define the spectrum, incidence, and risk factors for HIV-related sequelae (e.g., coinfections such as TB, HCV, and HPV, malignancies, and organ system-specific manifestations such as renal disease, eye disease, urologic and neurological conditions) in adult, adolescent, and pediatric populations specific to individual regions in diverse geographic settings.
- Determine optimal ways of integrating treatment for HIV and treatment for opportunistic infections and coinfections, especially TB, including clinical research to assess clinical outcome and operational research to determine cost-effectiveness.
- Investigate sustainable strategies for preventing, treating, and monitoring response to treatment of endemic coinfections in HIV infected adults, adolescents, children, and infants in resource-constrained settings.
- Assess the impact of available antibiotic treatment and prophylaxis regimens to optimize therapeutic approaches for TB and other endemic coinfections in the context of ART, including new therapies for TB and new approaches to administering drugs.
- Determine the safest and most efficient treatment modalities for endemic diseases (e.g., TB, HCV, and malaria) in the adult, pediatric, and adolescent populations infected with HIV.
- Develop methods to monitor development of antimicrobial resistance by HIV-related and endemic pathogens infecting both study participants and the general population.
- Develop strategies to enhance and monitor adherence to therapy/prophylaxis for endemic coinfections in HIV infected individuals.
- Determine the safety and effectiveness of available immunizations for endemic pathogens in diverse HIV infected populations.
- Develop simple clinical algorithms for guiding initiation of prevention or treatment of HIV-related coinfections and opportunistic infections.
- Assess the burden of TB and the relative importance of reactivation versus *de novo* infection in HIV-coinfected individuals in various settings.

- Identify affordable strategies to target high-risk patients for initiation of prophylaxis for HIV-related coinfections and OIs.
- Conduct studies to better understand the role and mechanism of reinfection and/or superinfection with HCV in coinfecting individuals.

**OBJECTIVE-I**

**Evaluate the impact of prevention and treatment programs on the HIV epidemic, taking advantage of comprehensive health service delivery programs related to HIV/AIDS.**

(The scientific objectives of C through I are of equal weight.)

**STRATEGIES**

- Assess the impact of ART on risk behaviors, HIV transmission and prevalence, including associated behavior change, in various communities.
- Determine the social, psychological, societal, and economic impact of ART on individuals (including children), families, and communities, including the impact on personal risk behaviors.
- Determine the impact of ART availability on utilization of VCT in various communities.
- Determine the impact of ART availability on entry into care and treatment.
- Determine whether expanded ART care and treatment leads to a decrease in HIV-associated stigma and discrimination.
- Determine effective strategies for integrating the delivery of HIV care with drug treatment, alcohol treatment, TB treatment, and other medical and social services commonly needed by HIV infected individuals.
  - ▶ Evaluate the impact of interactions between HIV therapeutics, alcohol, drug abuse, or medications used for the treatment of substance abuse on the maintenance of anti-addiction therapy and on MTCT.
- Determine the impact of ART on breastfeeding behaviors.
- Identify morbidities in HIV-exposed, noninfected infants and young children, using appropriate control populations, in resource-constrained settings.
- Study the direct effects of ART on HIV transmission, e.g., by evaluating the effectiveness of specific ART strategies in curtailing HIV transmission in HIV-discordant couples.
- Determine the public health impact of ART, specifically the likelihood of transmission of drug-resistant virus and the natural history of disease in people infected with a drug-resistant HIV strain.
- Examine the potential use of HIV therapeutic vaccines.
- Determine the impact of ART on the development of drug-resistant strains of HIV in diverse geographical settings, and develop strategies to limit its development. Develop biomarkers that can serve as surrogates for measurement of HIV risk behavior and can be used to predict and monitor rapid escalation of HIV subepidemics.
- Integrate operational and health services research with clinical research to facilitate the translation of research findings to clinical practice and public health programs and to provide information to inform the scaleup of HIV prevention, care, and treatment programs.
  - ▶ Develop strategies to ensure that prevention efforts in resource-limited countries are simultaneously preserved and enhanced when treatment clinical trials and, later, ART treatment programs are established.
  - ▶ Conduct research on how best to deliver prevention education in the care and treatment setting, targeting interventions to both HIV uninfected and infected individuals.

- ▶ Develop culturally appropriate mechanisms to identify persons for whom treatment is indicated and to overcome factors such as stigma and discrimination, which can forestall testing and limit the provision of treatment and care.
- ▶ Develop links with other agencies and organizations to integrate research with service programs and to develop multidisciplinary prevention research in multiple settings, including medical treatment and community support and care organizations.

## CHAPTER 5

# Research Support and Dissemination



**AREA OF EMPHASIS**

# Training, Infrastructure, and Capacity Building

**SCIENTIFIC OBJECTIVES AND STRATEGIES****OBJECTIVE–A**

Provide training domestically and internationally in biomedical, social, and behavioral research on HIV, with an emphasis on multidisciplinary research in racially and culturally diverse settings domestically, and with attention to the needs of marginalized communities domestically and in developing countries with high incidence and/or high prevalence of HIV infection.

**STRATEGIES**

- Increase predoctoral, doctoral, postdoctoral, and advanced research training across a broad range of AIDS-related disciplines.
- Support multidisciplinary training and mentoring programs to strengthen HIV/AIDS intervention research including behavioral interventions, vaccines, microbicides, therapeutics, sexually transmitted diseases in the context of HIV infection, interventions to interrupt mother-to-child transmission (MTCT), nutritional interventions, and substance abuse prevention and treatment.
- Expand the NIH AIDS Loan Repayment Program to bring minority U.S. scientists and physicians to the NIH in order to increase the cadre of trained HIV/AIDS researchers.
- Expand programs for HIV/AIDS research to develop culturally appropriate and relevant training and mentoring models to conduct research at U.S. minority-serving institutions.
- Develop and implement programs at domestic institutions, with attention to institutions serving minorities, to provide precollege training to attract students interested in behavioral and biomedical sciences related to HIV/AIDS research.
- Expand the number of domestic HIV/AIDS minority supplement awards to enhance the research capacity of minority individuals to make them more competitive for independent funding.
- Increase the number of funded U.S. minority investigators, for greater involvement and leadership in HIV research.
- Support HIV/AIDS research planning and organizational grants targeting domestic minority institutions and minority-serving communities. Emphasis should be placed upon grants that develop academy-community partnerships.
- Enhance opportunities through all Institutes and Centers (ICs) and programs to improve mechanisms for recruiting, training, mentoring, and retaining biomedical, behavioral, and social scientists in the conduct of interdisciplinary sex and gender analyses in HIV/AIDS research.

- Provide new opportunities and programs to attract newly trained investigators and established researchers from other fields to pursue HIV/AIDS research.
- Develop funding mechanisms to foster better linkages across AIDS-related scientific disciplines, including basic, clinical, epidemiologic, statistical, social, and behavioral science.
- Increase HIV/AIDS funding for the development of equal and productive partnerships between U.S. minority and majority institutions and community-based organizations (CBOs), with the funds located at the U.S. minority institution.
- Increase training to strengthen local capacity to conduct multidisciplinary AIDS-related prevention, vaccine, and therapeutic research in developing countries and emerging democracies by scientists from these countries.
- Strengthen cultural competency training and ethical training for the conduct of HIV/AIDS prevention, vaccine, and therapeutic clinical trials in domestic and international vulnerable populations.
- Provide support for all HIV/AIDS training materials such as CD- and Web-based training and training sessions; all training materials must be adapted for local languages.
- Provide training in Good Laboratory Practices (GLP)/Good Clinical Practices (GCP) for translational processes and in product development in both domestic and international settings conducting HIV/AIDS clinical trials or research.
- Implement new funding mechanisms to provide research training to nonphysician professionals (i.e., physician assistants and nurse practitioners) to increase the pool of HIV/AIDS minority researchers at domestic sites and at resource-poor settings.
- Support the training of biomedical and behavioral scientists in both developed and developing countries in the use of advanced computer and information technologies for HIV-related research, and ensure access to appropriate tools and equipment at the end of training.
- Support veterinary residency training programs in primate medicine at National Primate Research Centers (NPRCs) or other primate facilities to help to increase the number of highly trained veterinarians who can manage the increasing needs for HIV/AIDS nonhuman primate (NHP)-dedicated colonies.
- Support the training of veterinarian scientists who contribute to the growing need for interdisciplinary-trained researchers who help to understand both the microbial/infectious disease aspects as well as the animal model side of HIV/AIDS research in NHPs.
- Develop new models of integrated training that focus on the protection of human and animal subjects enrolled in HIV/AIDS clinical trials and on ethical issues of clinical trial design and implementation of vaccine and other prevention modalities in at-risk populations, in both domestic and international settings.
- Support training programs for personnel in resource-poor-setting institutions to strengthen the administrative and financial management capacity needed to conduct HIV/AIDS-related research.
- Expand programs to increase opportunities for scientists from developing countries and emerging democracies trained through the NIH to conduct AIDS research in their home countries (e.g., reentry grants).
- Develop new funding mechanisms and expand existing grant mechanisms, to link U.S. AIDS research scientists, industry partners, and relevant institutions with each other and with investigators and institutions in both developed and developing countries.

- Take advantage of existing AIDS clinical trial infrastructures to develop specific training programs in clinical trials methodology, including issues related to the design, recruitment, retention, target population dynamics, and analysis of data.
- Expand training programs on the effective use of HIV/AIDS antiretroviral drugs and prophylactic and therapeutic interventions for coinfections/opportunistic infections as well as adequate monitoring for patient safety.
- Develop training to prevent transmission of HIV and HCV in resource-poor health care facilities, including recruitment and retention of appropriate blood donors, predonation counseling of all blood donors, improvement of blood screening strategies and technologies, and appropriate use of transfusion.
- Support training opportunities for HIV prevention researchers interested in adding specific methodological skills to their research expertise (e.g., methods to conduct cost-effectiveness analyses, measurement of biologic outcomes in behavioral intervention studies, appropriate use of behavioral and social science measures in clinical trials, ethnographic and other qualitative methods, and network analysis).
- Support the training of members of HIV/AIDS-affected communities, to strengthen their ability to be informed partners in biomedical and behavioral science research.

## **OBJECTIVE-B**

**Establish and maintain the appropriate infrastructure needed to conduct HIV research domestically and internationally with emphasis on populations of high prevalence.**

## **STRATEGIES**

- Invest and expand funding in research infrastructure at U.S. minority-serving institutions to increase capacity to support HIV/AIDS research.
- Enhance, improve, and maintain research capacity and infrastructure in resource-poor settings with high HIV incidence, with particular emphasis on construction and operation of facilities for research on HIV prevention, including the development of vaccines and microbicides, as well as clinical trials for therapies and behavioral interventions.
- Enhance and improve the clinical trial research infrastructure for the conduct of prevention, vaccine, and therapeutics trials in domestic and foreign sites, including laboratory capacity, trained scientists and other personnel, appropriate participant cohorts, and mechanisms to address ethical issues such as the implementation of ethical committees and translated human rights documents.
- Enhance and improve research capacity and infrastructure to advance research on AIDS-associated coinfections (HCV, Kaposi's sarcoma-associated herpesvirus or human herpesvirus type 8, human papillomavirus, Epstein-Barr virus [EBV], tuberculosis [TB], and malaria) and associated malignancies.
- Support an adequate infrastructure for producing HIV/AIDS vaccine candidates, for preventive and therapeutic vaccine trials, under Good Manufacturing Practices (GMP).
- Support adequate facilities and resources as well as appropriate ethical and procedural training to conduct HIV-related research in animal models.
- Expand the production of genetically defined specific pathogen-free (SPF) NHP, with emphasis on Indian-origin rhesus macaques.
- Develop and characterize appropriate reagents for use in HIV-related research conducted in different species of macaques and also other NHPs.
- Maintain programs that enhance the current research infrastructure, particularly the trans-NIH infrastructure, such as the Centers for AIDS Research (CFARs), the Research Facilities Improvement Program, the NPRCs, and the General Clinical Research Centers.
- Provide support for, and awareness of, the Biomedical Technology Resources Program for structural studies of HIV proteins and host proteins in the context of HIV infection.
- Provide for the long-term support of advanced in-country research in resource-poor settings participating in priority AIDS-related intervention research, such as methods to interrupt mother-to-child, sexual, or parenteral transmission, or trials of candidate HIV vaccines.
- Increase collaboration between CBOs and other Government-supported service providers (such as those funded through HRSA, the U.S. Department of Veterans Affairs, and CDC) and academic researchers, to improve the quality and capacity of HIV/AIDS research endeavors in service settings.
- Establish and support quality-controlled repositories for, and ensure access by, qualified scientists to human samples (i.e., serum, peripheral blood mononuclear cell, plasma, patient-derived cell lines, cerebrospinal fluid,

semen, breast milk, lymphoid tissues, and other key patient samples) and HIV strains from clinical trials and natural history and epidemiological studies, especially in complex study settings (e.g., MTCT studies).

- Develop, maintain, and effectively utilize domestic and international cohorts, repositories, and nested studies among populations experiencing emerging and ongoing HIV epidemics to establish databases that support analyses of host and viral characteristics.
- Maintain the present AIDS-related tumor registries, and ensure linkages between AIDS and cancer registries, for both domestic and international studies.
- Improve and adequately disseminate the process of requesting, prioritizing, and receiving HIV/AIDS laboratory samples, so that access is as timely and equitable as possible.
- Promote Internet connections and availability of pertinent information technology at health science centers, hospitals, outpatient clinics, CBOs, and other access points, both domestically and internationally, for HIV-related research and patient care.
- Develop statistical sampling methodologies, data collection protocols, and statistical analysis tools that are easy to use and adaptable to different settings; facilitate efficient statistical analysis and report generation and enhance standardization, when appropriate, in the context of HIV/AIDS research.
- Promote research in, and application of, medical informatics (e.g., high-performance computing) for HIV/AIDS research and clinical practice in resource-poor settings, both domestically and internationally.
- Enhance coordination and collaboration among NIH-supported investigators, other U.S. Government agencies, and other international agencies conducting HIV/AIDS research in the same developing countries.
- Develop efficient and effective systems for collecting and managing HIV/SIV (simian immunodeficiency virus)/SHIV (chimeric simian/human immunodeficiency virus) multiple-center and single-site clinical and animal model trial data; ensure timely and accurate dissemination of clinical and animal model trial information.



## AREA OF EMPHASIS

# Information Dissemination

## SCIENTIFIC OBJECTIVES AND STRATEGIES

### OBJECTIVE–A

**Support the effective dissemination, communication, and utilization of HIV/AIDS information to all constituent communities of the NIH, domestically and internationally.**

### STRATEGIES

- Rapidly disseminate new research findings, including information on the potential implications for prevention, care, and treatment of HIV infected individuals, using existing and innovative methods.
- Facilitate the development of HIV prevention and treatment guidelines based on the latest clinical research findings.
- Utilize computer and other information dissemination technology (including the Internet) to disseminate up-to-date HIV/AIDS information; information about HIV therapeutic, vaccine, microbicide, and prevention trials; and information about HIV training programs.
- Expand access to and education about current state-of-the-art treatment and patient management guidelines, including information on clinical trials, using multiple technologies such as online access and voice access (AIDSinfo).
- Improve current techniques and develop and evaluate new techniques for the two-way communication of information to scientific and lay audiences, particularly to hard-to-reach populations, including information about clinical trials.
- Improve outreach and support access to HIV/AIDS information resources (including computers) by community groups, health care providers, and community-based HIV/AIDS service organizations, including those serving minority communities.
- Work with community-based organizations (CBOs) to develop and promote effective methods of information dissemination in target populations.
- Work with CBOs, professional organizations, and local agencies to promote the use of current, high-quality information on treatment, prevention, and research.
- Support dissemination of information, including to constituent communities, in culturally and linguistically appropriate ways.
- Develop and disseminate educational information to enhance understanding of HIV and basic and clinical research processes by health care providers, community-based HIV/AIDS service organizations, social service organizations, policymakers, and persons with HIV/AIDS.

- Develop and disseminate information resources about HIV vaccine clinical trials and the importance of potential HIV vaccines.
- Evaluate the effectiveness of communication efforts by appropriate means, including obtaining feedback from target audience members through such methods as usability testing of paper and computer interfaces (see [www.usability.gov](http://www.usability.gov)) and information dissemination intermediaries, such as journalists and health educators.
- Promote wide dissemination of the annual *NIH Plan for HIV-Related Research* and other HIV-related reports as they become available.
- Promote and enhance the exchange of scientific information and communication between public and private research enterprises, such as enhancing communication with the pharmaceutical industry concerning research on the development of therapeutics, vaccines, and microbicides, and working with industrial scientists to make information concerning basic science and HIV protein structures available to the general scientific community.
- Communicate and exchange information internationally on topics such as prevention and treatment, patient management guidelines, and research results that improve the care of HIV infected individuals, including those in developing countries.
- Support the exchange of basic and applied research information at community, regional, national, and international conferences and workshops.
- Support the cross-collaborations of HIV/AIDS information providers to develop more integrated and comprehensive information dissemination approaches.
- Provide online access to presentation materials, including full text of abstracts and other information (e.g., slides, graphics, plenary presentations) from scientific meetings.
- Collect, archive, and promote use of existing data from NIH-supported basic and applied research for secondary data analysis, including rapid development of public use data sets that can be used for secondary data analysis in NIH-supported studies, especially baseline survey and HIV/STD (sexually transmitted disease) incidence data.
- Widely disseminate information concerning specimen repositories, including existing repositories, specimens available, and relevant information concerning cohorts, contact information, and the process for obtaining access to samples.

**OBJECTIVE–B**

Support research to identify existing gaps in communication approaches, identify and evaluate existing strategies, and develop and test new and innovative communication strategies that will improve access to and use of state-of-the-art HIV information by all relevant target audiences, domestically and internationally.

**STRATEGIES**

- Assess the information needs and resources used by various audiences, including biomedical and behavioral research communities, health care providers, service providers, persons living with HIV and their advocates, at-risk populations, scientific and lay media, and the general public.
- Identify obstacles to information dissemination and develop, test, and evaluate possible ways to overcome these obstacles.
- Develop, test, and evaluate innovative strategies for effectively reaching specific audiences (e.g., minority communities, adolescents, drug users, other hard-to-reach populations, and health care providers) with relevant HIV information.
- Investigate how and under what circumstances different communication and dissemination strategies influence the adoption of scientifically based HIV behavior-change interventions and clinical practices in specific audiences.
- Promote use of new technologies and evaluate their effectiveness for disseminating basic and clinical research findings.
- Work to reduce communication gaps between academic researchers and treatment providers so that research results are more effectively disseminated to providers and that research agendas reflect the needs of practicing clinicians.

## **OBJECTIVE–C**

**Develop, implement, and evaluate methods of coordination and collaboration on HIV/AIDS communications activities among NIH Institutes and Centers (ICs) and with other Federal and non-Federal groups.**

## **STRATEGIES**

- Build and enhance partnerships among CBOs and basic, clinical, and behavioral researchers to encourage exchange of information and experience.
- Promote and foster information dissemination regarding research and programmatic efforts across the ICs, among U.S. Government agencies, and with international partners.
- Promote collaboration among all ICs in providing information about their HIV/AIDS clinical trials to AIDSinfo and ClinicalTrials.gov.
- Expand the development of HIV/AIDS resources on the Internet to facilitate national and international research collaboration and data sharing.
- Continue collaborations with the Joint United Nations Programme on HIV/AIDS, the Pan American Health Organization, and other international AIDS agencies or societies on information/communications efforts, including information about international clinical trials.
- Collaborate with public and health sciences libraries, health care providers, AIDS Education and Training Centers, and community-based HIV/AIDS service organizations to facilitate access to needed information.
- Expand collaboration to include academic, medical, and other communities, as appropriate, in the dissemination of NIH HIV-related reports.



Office of AIDS Research, National Institutes of Health  
U.S. Department of Health and Human Services  
5635 Fishers Lane, Room 4000 (MSC 9310)  
Bethesda, Maryland 20892-9310  
Tel: 301-402-8655, Fax: 301-402-8638